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MODERN MEDICINE

ITS THEORY AND PRACTICE

IN ORIGINAL CONTRIBUTIONS BY AMERICAN AND FOREIGN AUTHORS

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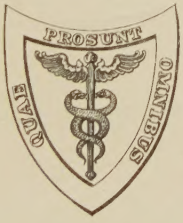
VOLUME II

DISEASES OF DOUBTFUL ETIOLOGY—DISEASES CAUSED BY PROTOZOA, SPIROCHETES, AND ANIMAL PARASITES—DISEASES DUE TO PHYSICAL, CHEMICAL, AND ORGANIC AGENTS—DEFICIENCY DISEASES

ILLUSTRATED



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PART I

DISEASES OF DOUBTFUL OR UNKNOWN ETIOLOGY

CHAPTER I

SMALLPOX

By E. J. G. BEARDSLEY, M.D.

Smallpox (Latin, Variola; French, La petite Verole or La Variole; Italian, Vajuola; German, Blattern or Pocken) is an acute infectious disease characterized by a sudden onset, usually with a chill or chilly sensations and a febrile stage of three or four days' duration, during which period the patient usually complains of headache, dizziness, backache, general body pains, gastric distress and vomiting. On the third day of the disease a general minute, macular eruption appears which, in the succeeding eight days, passes through the stage of papule, vesicle, pustule and crust. After recovery the site of the cutaneous lesions is marked by scars the extent and depth of which depend upon the character of the original pustules.

This disease is the most characteristic of the acute exanthemata, and in no other disease do the various stages of eruption succeed one another with such unchanging regularity. This is apparent in the literature, for the clinical descriptions from Sydenham to the present day show great similarity and there has been but little added to the description given by Sydenham over two hundred and fifty years ago.

The disease is entirely preventable and so great is the protection given by vaccination and revaccination that a majority of physicians have never seen a case of smallpox in private practice. The disease is infrequently seen in most communities but its presence throughout the world is continued by the ignorant or the careless. The floating, irresponsible population who do not usually acquire a residence and therefore are frequently not subject to vaccination laws are often responsible for epidemics. The outbreaks of the disease are also encouraged by a class of citizens with that peculiar order of mind which renders them incapable of sane judgment regarding health matters and who seek in every way possible to oppose vaccination not only for themselves but for others. One of the saddest features in connection with smallpox is that in every epidemic there are a number of unvaccinated children and others in no

way personally responsible, who die of the disorder or are permanently disfigured or blinded. Ker states the matter well in the following words: "So long as vaccination and revaccination cannot be universally enforced, smallpox will continue to be with us, unfortunately also, will continue to be the cause of most regrettable loss of life and waste of money."

The members of the medical profession should bear in mind that much of the widespread prejudice, even among intelligent citizens, against vaccination is sometimes based upon the unfortunate results of carelessly performed vaccination and poorly treated vaccination wounds. It is regrettable that the profession has not universally adopted a method of vaccination, such as acupuncture, that would, in a large measure, eliminate the danger of infection of the vaccination wound. Until vaccination wounds are much less frequently infected and until tetanus infection following vaccination is unheard of, the medical profession must sympathize, to a certain extent, with those individuals who are prejudiced against vaccination.

Incidence.—No acute infectious disease shows such a complete independence of conditions of race, age, sex, climate and soil as does smallpox. It thrives equally well wherever its contagion may be carried and where it finds a susceptible population. The susceptibility of the population varies. During and after each appearance of smallpox in a community, vaccination is carried out vigorously and efficiently and the susceptibility is diminished or rendered *nil* by vaccination or by an attack of the disease. With the passing of the disease, vigilance relaxes and the number of susceptible individuals increases both by birth and by the advent of unvaccinated persons from other communities. The disease is kept in existence by sporadic cases, and with this and susceptible individuals there will be an outbreak from time to time. There is an irregular periodicity in the outbreaks which is also shown in epidemics of the prevaccination period.

The *season* of the year has an influence on the morbidity and upon the diffusion of an epidemic. Rhazes, in his original description, stated that in Arabia epidemics occurred at all seasons, but generally began at the end of the autumn, in the early spring or in the cold season. There is much irregularity in the appearance of epidemics; in England, for instance, between 1837 and 1840 there were 9095 deaths in the winter, 9470 in the spring, 10,005 in the summer and 12,483 in the autumn. The epidemics in America of 1882 and 1902 reached their height in the winter and early spring.

Before the American occupation of the Philippines there were at least 40,000 deaths annually from smallpox. In 1902 a system of compulsory vaccination was introduced, In 1903 there were 1900 deaths from smallpox, 900 in 1904, 4000 in 1906, 3000 in 1910, 1000 in 1911 and less than 1000 deaths a year from 1912 to 1916. Then came a period in which vaccination was neglected and in 1918 there were 14,574 deaths and in 1919, 45,873. In 1918, 93 per cent. of the deaths due to smallpox in the Philippines occurred in persons not vaccinated. With another campaign of vaccination and revaccination there was a very prompt drop in the morbidity, as well as in the mortality rates, of this disease.

During recent years the epidemics of smallpox encountered in the United States have been, as a rule, of an unusually mild character and this is true of outbreaks of the disease in England and other countries. The following table from the Statistical Bulletin of the Metropolitan Life Insurance Co. illustrates the mildness of recent epidemics:

NUMBER OF SMALLPOX CASES AND DEATHS IN THE UNITED STATES AND IN CANADA, 1916 TO 1923

Area.	Cases.	Deaths.	Deaths per 100 cases.
United States:			
1923 (42 states and Dist. of Columbia)	25,943	163	0.6
1922 (42 states and Dist. of Columbia)	27,928	791	2.8
1921 (42 states and Dist. of Columbia)	91,335	657	0.7
1920 (47 states and Dist. of Columbia)	108,835	514	0.5
1919 (43 states and Dist. of Columbia)	58,348	328	0.6
1918 (39 states and Dist. of Columbia)	76,831	396	0.5
1917 (38 states and Dist. of Columbia)	47,507	313	0.7
1916 (30 states and Dist. of Columbia)	15,532	82	0.5
Canada:			
1923 (8 provinces)	1,383	3	0.2
1922 (8 provinces)	1,950	6	0.3
1921 (8 provinces)	6,713	37	0.6
1920 (8 provinces)	7,579	53	0.7
1919 (6 provinces)	5,635	25	0.4
1918 (4 provinces)	1,295	9	0.7
1917 (4 provinces)	605	7	1.2
1916 (3 provinces)	39	5	12.8

The following table illustrates the morbidity rates for five states, Massachusetts, New Jersey, Pennsylvania, Michigan and California:

	Massachusetts.	New Jersey.	Pennsylvania.	Michigan.	California.
1919	40	109	229	2,460	2,002
1920	29	182	215	4,845	4,480
1921	37	255	212	4,537	5,581
1922	2	18	85	1,231	2,129
1923	6	30	183	2,311	2,025
Total	114	594	924	15,384	16,217

In Pennsylvania, in 1924, 287 cases were reported for the months of January to September, inclusive. During the same period in New Jersey 310 cases with 6 deaths were reported. The mildness of recent smallpox infections in New Jersey is well illustrated by the fact that for the fifteen years previous to 1924, 1181 cases with but 6 deaths were reported.

Unfortunately, there are very real disadvantages, from a public-health standpoint, connected with this mildness of the disorder. It tends to overcome the healthy fear of the disease and prevents active prophylactic measures being instituted because public sentiment cannot be aroused in favor of them. As is so often true following a period in which only mild cases of the disease are encountered there have been a number of sharp outbreaks in 1924 of a very malignant nature and because of the unvaccinated condition of the citizens many lives have been lost.

It is interesting to note how frequently epidemics are initiated by the appearance of atypical cases of the disease. In May, 1924, an elderly man who had been visiting in Dwight, Ill., arrived in an isolated village

of Burlington County, N. J., extremely ill. He died five days later and the death certificate was signed "pyonephritis," contributory cause, "cardiac decompensation, septic erythema." Ten days after embalming his body the undertaker's assistant was taken ill with severe confluent smallpox from which he eventually recovered. A woman who had been exposed to infection from the first patient also developed the disease. It was later learned that the visitor from Illinois had been exposed to smallpox a few days before his visit to New Jersey. In an epidemic in Minnesota in January, 1924, the first patient was a male nurse, fifty-four years of age, who had never been successfully vaccinated and who died in two days. Subsequently there was a total of 182 for this epidemic and 139 of the individuals who contracted smallpox had never been vaccinated. Of these 139 unvaccinated individuals 34 died. Another such epidemic occurred in Windsor, Ontario, in February, 1924, in which a man became acutely ill. He was seen by four physicians, two being consultants, and the condition was thought to be an unusually severe attack of purpura hemorrrhagica. The patient died promptly and it was not until those who came in contact with him were stricken with similar symptoms that the true diagnosis, hemorrhagic smallpox, was made. In this epidemic there were 67 cases with 32 deaths. Eleven of the cases were atypical and several died before the true nature of the disease was discovered.

WINDSOR EPIDEMIC

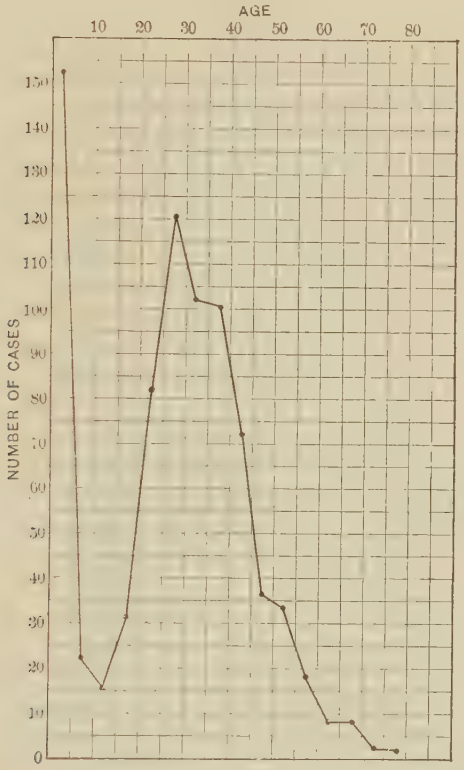
	Cases.	Deaths.	Mortality per cent.
Never successfully vaccinated	45	32	71
Vaccinated successfully twelve to sixty-five years before	10	0	0
Vaccinated successfully during incubation period, *i. e.*, became ill with smallpox when they had a "taking" vaccination	12	0	0

In a smaller outbreak in Ontario of 9 persons affected, 3 died. From one of the atypical cases in this epidemic another community was infected and 24 patients contracted the disease of whom 22 had never been vaccinated. The 2 patients who had been vaccinated had intervals of eighteen and thirty-five years since vaccination. It is not certain that children are naturally more susceptible than adults. The cases among them decrease in frequency after the tenth year, owing to compulsory vaccination to obtain school privileges. The chart on page 21 illustrates the influence of vaccination at the school age.

The mortality seems to be greater during the height of an epidemic that in its decline. It varies greatly in different epidemics and this is equally true of the epidemics in the prevaccination period and in modern times. From 1901 to 1903 there were epidemics in parts of the United States in which the mortality was as low as 2 per cent. The death-rate from smallpox in Massachusetts during these years was 11 per cent. while in Philadelphia in the same period was a mortality of 26.89 per cent. in 7204 cases. Previous to the extremely mild epidemics of recent years the mortality in patients under one year of age was extremely high because no protection had been afforded by vaccination.

Race seems to exert little influence upon the morbidity or mortality. When the disease is introduced into aboriginal tribes the mortality is extremely high. The first outbreak of smallpox in the Western hemi-

FIG. 1



Curve of ages of 800 cases of smallpox. Notice the extraordinary decline at eight years. (School vaccination.)

AGE DISTRIBUTION OF SMALLPOX CASES IN CALIFORNIA, 1916 to 1921

Ages.	Number of cases.					Per cent of total.				
	1916.	1918.	1919.	1920.	1921.	1916.	1918.	1919.	1920.	1921.
Under 5 . . .	25	41	144	341	392	12.2	6.3	9.2	8.1	7.4
5 to 9 . . .	34	104	281	722	966	16.6	15.9	18.0	17.1	18.3
10 to 14 . . .	16	87	250	757	1060	7.8	13.3	16.0	17.9	20.1
15 to 19 . . .	16	78	178	408	628	7.8	11.9	11.4	9.7	11.9
20 to 24 . . .	23	49	118	292	354	11.2	7.5	7.6	6.9	6.7
25 to 34 . . .	41	110	189	570	607	20.0	16.8	12.1	13.5	11.5
35 to 44 . . .	30	117	222	602	685	14.6	17.9	14.2	14.3	13.0
45 to 64 . . .	16	65	159	468	516	7.8	9.9	10.2	11.1	9.8
65 and over . .	4	3	19	58	70	2.0	0.5	1.2	1.4	1.3
All ages . . .	205	654	1560	4218	5278	100.0	100.0	100.0	100.0	100.0

sphere occurred in the West Indies in 1507, and entire tribes were exterminated. When the disease reached Mexico from Spain in 1520 the number of deaths due to it has been estimated at 3,500,000. In the epidemics in this country, cases are relatively more numerous among the negroes and the mortality among them is high. Both the increased morbidity and death-rate are due to the greater number of unvaccinated persons. Welch and Schamberg found a mortality of 49.45 per cent. in unvaccinated negroes, and 44.69 per cent. among white patients.

Etiology.—The etiology of smallpox is unknown. No bacterium peculiar to the disease has been found; in many cases it is not possible to demonstrate bacteria microscopically or culturally in the specific lesions; when bacteria are found they are present in the advanced pustules rather than in the young and developing lesions. The supposed organism is, at present, grouped with the filterable viruses.

The included bodies in the epithelial cells of the specific lesions, which have played an important role in the attempts to discover the etiology, were first described by Weigert in 1874. Guarnieri, in 1892, gave the first clear description of the bodies which he regarded as parasitic protozoa and believed to be the specific cause of both vaccinia and smallpox. He gave the organism the name "*cytoryctes variolæ*," the name having reference to the supposed property of the organism of devouring the epithelial cells and in this way forming a space within which the organism lies. Later, Wasielewski, Magrath, Brinckeroff, Councilman and others confirmed their presence in smallpox and regarded these bodies as protozoan parasites and as the specific cause of the disease. Although the "*cytoryctes variolæ*" are constantly found in the lesions of both human and experimental smallpox their exact etiological significance has not been definitely ascertained. Prowazek states that the bodies are not protozoal, but considers that they may be due to nuclear changes due to a specific action of the virus of variola upon the epithelial cells. Other investigators have favored the view that the "*cytoryctes variolæ*" are not protozoan but are degenerative products produced by the virus of the disease.

Pathology.—**The Mucous Membranes.**—The specific lesions in the mucous membranes show a general resemblance to those of the skin, although there are modifications due to the differences in the tissues. The epithelial cells are in much looser connection with each other, the tissue is more easily permeated by the exudation, and the horny layer is absent. The specific character of the lesion is apparent only in a very early stage. The epithelial cells first affected, together with the cells adjacent to them, are thrown off by the exudate, leaving an area bare of epithelium. The lesions develop in the same way as in the skin by the infection and degeneration of circumscribed foci of epithelial cells followed by exudation. The hyaline fibrinoid degeneration takes place as in the skin. In addition to the specific lesions in which the alleged parasites are found, there are more serious lesions which are non-specific, and at autopsy most frequent in the soft palate and uvula. They consist chiefly of superficial loss of substance with deep necrosis of the underlying tissue. In such lesions masses of streptococci are found. The specific eruption may be found in

the mucous membrane of the mouth and fauces in the larynx, more rarely in the trachea and bronchi and in the œsophagus not infrequently. In only 1 out of 54 examinations was a specific lesion with the parasitic inclusions found in the mucous membrane of the stomach. In 2 cases a pustule was found in the penile portion of the urethra. None were found in the vagina or in the female urethra.

Lungs.—The most common lesion is bronchitis, usually with more or less extensive bronchopneumonia. Both the large and small bronchi are affected. In 54 autopsies by Councilman such lung lesions were found in 43 and lobar pneumonia was found in 2 cases. In 8 cases the lung exudate was largely hemorrhagic, and in 4 cases of purpuric smallpox, hemorrhages were found in both lungs and on the pleura without any evidence of pneumonia. Different varieties of pyogenic cocci are constantly found in both bronchitis and bronchopneumonia. The streptococcus is most common and next the pneumococcus. The lung lesions are found in all stages of the disease from the earliest to the latest. They are the most common and most serious complications. In many cases the lung lesions are so extensive as to be a sufficient cause for death without the specific disease.

Liver.—The liver is generally enlarged, this being most marked in the late pustular and crusting stages. This increased weight is ascribed to the swelling of the cells, which are larger and more granular than normal. The liver in typhoid fever is regarded as the classical type of cloudy swelling, but the increased weight in typhoid (average 1893 gm. in 64 cases) is slight compared with that in smallpox. The fat of the liver is not increased.

Spleen.—This organ is commonly enlarged in the early as well as in the late pustular stages. The spleen differs in smallpox from that of other acute infections in the great diminution in number or the absence of polynuclear leukocytes. In the hemorrhagic forms, and in the early period of the ordinary types up to the completion of the pustular stage, it contains in some cases no recognizable polynuclear leukocytes. In the period of desquamation, they are fairly abundant.

Lymphatic Glands.—The lymph nodes are swollen in the beginning of the disease; the swelling persists or increases during the period of eruption, and then slowly diminishes. The most common condition is a general œdema producing dilatation of the sinuses and separation of the cells of the follicles. The enlargement of the nodes is due more to this œdema than to cellular hyperplasia. Numbers of large basophilic cells are found both in the sinuses and in the follicles. Phagocytic cells are always present; they are most numerous in the latter stages of the disease, and are confined chiefly to the sinuses. They are formed by the proliferation of the endothelial cells. Streptococci are frequently found in the sinuses.

Bone-marrow.—Chiari, in 1893, investigated the marrow in 22 cases embracing all stages of the disease, and found changes in 86 per cent. He described under the name "*osteomyelitis variolosa*," foci of necrosis and hemorrhage associated with the presence of large cells. The necrosis of the bone-marrow has been studied by later investigators, notably Councilman, Mallory and Debeyre, and Chiari's original observations

have been confirmed. There seem to be two distinct forms of osteomyelitis complicating smallpox: (1) The pyogenic metastatic osteomyelitis that occurs in other infectious diseases, and (2) a distinct form of necrosing non-suppurating osteomyelitis probably due to the specific virus of smallpox, which frequently involves the diaphyseal ends of the long bones, destroying the epiphyseal lines and causing late deformities. The specific form of osteomyelitis associated with smallpox is most frequent in children. It is not recognized during the acute clinical stage as osteomyelitis, and the early deformities are frequently overlooked because the evolution of the lesion is so gradual.

Testicle.—The lesions most difficult to interpret are those affecting the testicle. There is absence of spermatogenesis save in the cases in which convalescence is established. Normal spermatozoa are absent in the lumen of the tubules and there is degeneration of the spermatogenic cells. This affects both the cytoplasm and nuclei, and the degenerating nucleus assumes forms which present some similarity to certain of the alleged intranuclear parasites in the epithelial cells of the skin. In addition to these diffuse degenerative lesions, there are focal lesions as characteristic of the disease as the skin lesions, which are found in the undeveloped testicles of children and in the adult. The lesions begin as an infiltration of the intertubular tissue with ordinary lymphoid cells and large mononuclear basophilic cells. From such lesions, which are best compared with small interstitial foci in the kidneys, the process extends. The area enlarges, the cellular infiltration extends, and finally there is complete necrosis in the centre, with fibrin and hemorrhages in the surrounding interstitial tissue. The lesions vary in number, some testicles showing large numbers, while in others they are found only after a prolonged search. The lesions show a general relation to the duration of the disease, the most advanced cases occurring late in the disease. In spite of the fact that such lesions seem to be specific to smallpox no cytoryctes are found in the testicular lesions of man.

Kidney.—Unrah, in 1872, first called attention to hemorrhages into the kidney pelvis in smallpox and found this in 28 of 212 cases. Councilman found it in 5 of 54 cases. The hemorrhage takes place beneath the mucous membrane. This lesion is found in cases in which there are hemorrhages into other organs and has no relation to hemorrhagic nephritis, a rare complication of smallpox. The hemorrhage is confined to the mucous membrane of the pelvis and does not extend into the ureters and bladder. In cases of hematuria during an attack of smallpox, not otherwise complicated, this pelvic hemorrhage seems the most probable source of the blood. The kidneys are affected in all cases; the most common change is acute degeneration of the epithelium, which occurs at all ages and in all stages of the disease. The kidneys are usually enlarged, rather œdematous, and opaque on section. In 5 of 54 cases, acute glomerulonephritis was found, and in one it developed during convalescence.

Heart.—The lesions are usually myocardial, either degenerative or true inflammatory processes. In 3 cases studied by Councilman, 2 being examples of purpuric smallpox, well defined foci of degeneration were

found in the cardiac muscle. Yellow, flabby and brittle heart muscle was a common finding in the subjects that died as the result of malignant forms of smallpox. Councilman found but 1 case of acute vegetative endocarditis in 54 autopsies. Endocarditis is a relatively rare finding as is pericarditis.

Inoculation Smallpox.—Although at the present time the chief interest of this form of the disease is concerned with its history we must not fail to remember that previous to the introduction and adoption of preventive vaccination inoculation smallpox was of great importance. This form was produced by the direct inoculation of the vesicle or pustule contents from a patient suffering from smallpox to an individual who was to be protected from natural smallpox by preventive inoculation.

Inoculation smallpox differed materially in its symptomatology and behavior from true smallpox. The period of incubation was eight days instead of twelve to fourteen and the resultant disease was, as a rule, incomparably milder than, so called, natural smallpox. The practice of inoculation to bring about protection from natural smallpox seems to have been of great antiquity. It had been noted that a person was seldom affected with smallpox a second time but when and how the method of artificially inducing the disease was discovered is unknown. According to tradition inoculation was a most ancient custom in India, France and Italy and had been secretly practised by the peasants from time immemorial.

Crookshank quotes Dr. Richard Mead as favoring the view that inoculation was first employed by the natives of Circassia. Mead's words are: "I have often wondered how such a notion could come into the heads of people almost quite ignorant of what relates to physic. For, as far as I have been able to find out by inquiry, this was the invention of the Circassians, the women of which country are said to excel in beauty; upon which account it is very common, especially among the poorer sort, to sell young girls for slaves to be carried away into neighboring parts. When therefore it was observed that they who were seized with this distemper were in less danger both of their beauty and their life the younger they were, they contrived this way of infecting the body so that the merchandise might bring the greater profit." De la Motraye, in 1711, saw inoculation performed upon a Circassian girl of four or five years of age. The girl, after being purged with dried fruit was inoculated from the contents of the pustules of another child suffering from natural smallpox. The inoculation was performed by old women and the results were, as a rule, very favorable, the patient passing through a mild attack of the disease.

The first publication in England giving a description of the custom of inoculating or ingrafting the smallpox was written by Kennedy in 1715. This surgeon had observed inoculation in Constantinople and was greatly impressed by its efficacy. Timoni and Pylarini, in 1717, described in detail the success achieved by the Turks with this preventive inoculation but the medical profession of England was persuaded to adopt variolous inoculation by Lady Mary Wortley Montagu, whose husband was ambassador at the Ottoman Court. In 1717, Lady Montagu wrote a

letter from Adrianople to a friend in England in which she expressed her determination to persuade the physicians in London to resort to inoculation. Her letter contains so much definite information regarding inoculation that it should be read by every medical man. "Apropos of distempers, I am going to tell you a thing that I am sure will make you wish yourself here. The smallpox, so fatal and so general among us, is here entirely harmless by the invention of ingrafting, which is the term they give it. There is a set of old women, who make it their business to perform the operation every autumn in the month of September, when the great heat is abated. People send to one another to know if any of their family has a mind to have the smallpox. They make parties for this purpose, and when they are met (commonly fifteen or sixteen together), the old woman comes with a nutshell full of the matter of the best sort of smallpox, and asks what veins you please to have opened. She immediately rips open that your offer to her with a large needle (which gives you no more pain than a common scratch), and puts into the vein as much venom as can lie upon the head of her needle, and after binds up the little wound with a hollow bit of shell; and in this manner opens four or five veins. The Grecians have commonly the superstition of opening one in the middle of the forehead, in each arm, and on the breast, to make the sign of the cross; but this has a very ill-effect, all these wounds leaving little scars, and is not done by those that are not superstitious, who chose to have them in the legs, or that part of the arm that is concealed. The children or young patients play together all the rest of the day, and are in perfect health to the eighth day. Then the fever begins to seize them, and they keep their beds for two days, very seldom three.

"They have very rarely above twenty or thirty (lesions) on their faces, which never mark; and in eight days they are as well as before their illness. Where they are wounded, there remain running sores during the distemper, which I don't doubt is a great relief to it. Every year thousands undergo this operation; and the French Ambassador says pleasantly that they take the smallpox here by way of diversion, as they take the waters in other countries. There is no example of any one who has died in it, and you may believe I am very well satisfied of the safety of the experiment, since I intend to try it on my dear little son. I am patriot enough to take pains to bring this useful invention into fashion in England; and I should not fail to write to some of our doctors very particularly about it, if I knew any one of them that I thought had virtue enough to destroy such a considerable branch of their revenue for the good of mankind."

In March, 1717, Lady Montague's son was inoculated and the progress of the induced disease was in every way favorable, about one hundred pustules resulting which healed with scarcely perceptible scarring.

Inoculation was not performed in England until 1721 and was at first looked upon with suspicion and fear. It was considered a dangerous experiment and it was not until there was an opportunity of studying the effect of inoculation upon a series of criminals in Newgate prison, who were promised a full pardon if they submitted to the experiment, that the favorable effects of the experiment were realized. The large

amount of variolous material which was, at first, considered necessary in inoculation brought about a danger in apparently infecting non-immunes with natural smallpox. In spite of prejudice and accidents in its use, inoculation soon earned for itself a place in medical practice throughout the world. There is an interesting history of an extensive use of inoculation carried out by a grandson of Lady Montague, William Stuart. While he was vicar of Luton, in Bedfordshire, a malignant smallpox epidemic broke out in that neighborhood and he, having absolute confidence in the practice, offered to have every person, who was uninfected, inoculated at his own expense. He had only a country practitioner and country nurses to depend upon but above 2000 persons were inoculated. Only 3 persons died: an infirm woman, a man past eighty years of age, and an infant whose mother afterward confessed she knew it had already been infected with natural smallpox, which in her ignorance, she supposed inoculation was to cure. For several succeeding years the smallpox scarcely reappeared in that district. With the discovery of the protective action of vaccination by Jenner in 1798 inoculation became no longer necessary. Circumstances may arise even now under which inoculation might become necessary, as when in the absence of any means for vaccination the exposure of unvaccinated individuals to the disease is inevitable. Inoculation, under such conditions, would be as practical as in the days of Lady Montague. Councilman reports a modern reference to inoculation by Plehn, who describes the process as now practised in central Africa. It is to be remembered that there is great difficulty in preserving vaccine virus in tropical countries while "natural" smallpox is still common in uncivilized lands. Plehn saw the upper arm used as the site of inoculation, and the contents of fresh smallpox pustules were introduced into incisions made with a sharp knife. The result was never a general infection with smallpox, but the formation of typical vaccine pustules which in no way could be distinguished from those produced by vaccination. In many cases a group of pustules formed about the site of inoculation and scattered pustules could be seen over other portions of the body. This observer never saw a serious illness result nor did he hear of a fatal infection due to this method. Notwithstanding the mildness of the disease so produced, there is, unfortunately, no diminution in the virulence of the virus which is produced in the lesions. A case of inoculated smallpox is just as able to transmit smallpox in its most virulent form as a case of "natural" smallpox. It was this danger that led to the prohibition of the practice of inoculation.

Symptoms.—The period of *incubation* has been more accurately determined in smallpox, owing to the suddenness of the onset, than in other infectious diseases. It is but rarely that cases suitable for this determination are seen and they are more apt to be associated with sporadic infections. The exposure must be but once and for a short time. A sufficient number of such cases have been recorded by competent observers and all agree in placing the time for incubation between ten and fourteen days in the great majority of cases. Welch and Schamberg saw cases in which it was sixteen days and one in which it appeared to be five and a half days. MacCombie recorded a case in which the incubation period

was seven days and Knecht saw a patient in whom only seven and a half days elapsed from exposure to the outbreak of symptoms. Armstrong cited a case in which the incubation period appeared to be extended to twenty-one days. In general the length of the incubation period is of no influence in determining the character of the disease. Zuelzer is of the opinion that in purpura variolosa, the period of incubation is shorter than usual being from six to eight days in 9 cases that he observed Usually during the period of incubation there are no symptoms, the individual being in perfect health.

The *initial stage* (the period between the onset and the appearance of the eruption) is found in practically all cases, and forms one of the most characteristic features; it is even more characteristic than the eruption, for this may be absent or atypical. The duration of the initial stage is usually three days. Bancroft found variations from this in 263 of 530 cases. In 7 the initial stage was absent or the symptoms were so slight as to be unnoticed; in 26 the symptoms lasted but one day, in 91 for four days, and in 139 for two days. Analysis of these cases showed no relation between the length of the initial stage and the severity of the disease.

The *onset* is usually sudden and marked by definite and severe symptoms, such as great depression, headache, backache, chill and vomiting; occasionally the symptoms are gradual in onset and accompanied by malaise, fugitive pains and gastric disturbances. The severity of the initial symptoms varies greatly and there is little relation between the initial severity and the character of the established disease, since very mild cases may begin with stormy initial symptoms. Mild initial symptoms, as a rule, preclude the more severe forms of the disease. The *depression* may be very marked; there is frequently great weakness and giddiness with disordered consciousness. Not infrequently individuals who are first affected on the streets are taken into custody by the police under the misapprehension that the affected person is intoxicated, and the true condition is not realized until the eruption appears. The depression is much greater than in the initial stages of typhoid fever or influenza, for early in an attack of smallpox the patient is, at times, unable to stand and frequently staggers as if drunk.

When brought to the hospital, the face of the patient appears sunken and pale, the features expressionless, the extremities cold, and the pulse small and frequent. The patient gives one the impression of one overwhelmed with toxemia. Children frequently have general convulsions at the onset. Other disturbances of the central nervous system are seen. Insomnia, in part due to pain and fever, is common even in the mild forms of the disease. Somnolence, sometimes to the extent of coma, is seen in uncomplicated cases, especially in children. Bancroft saw one child in the status epilepticus with constantly recurring convulsions for an entire day. Many patients complain of terrifying dreams, and attempt to keep awake to avoid them. Delirium is common, and is usually the type encountered in drunkards. In spite of the delirium the patient can, in many instances, be roused and answers questions intelligently only to return to the muttering delirium when not stimulated by ques-

tioning. Sometimes the most violently delirious suddenly become rational at the sound of an accustomed voice or unusual happening. Catatonia and sensory disturbances in the form of local anesthesia have been described by many observers. Bancroft met with disturbances of speech exclusive of those incidental to delirum, in 3 cases, in 1 consisting of a slight stammering and in 2 of a transitory aphasia lasting from the first to the fifth day of the disease.

Headache as an early symptom is common, unusually severe and often so sharp as to be so agonizing that patients make violent outcries and grasp or even strike the head. The pain may be confined to the forehead or temples or it may extend over the entire head. It is often described by patients as though a band were encircling the head, or as a lancinating, throbbing and sickening pain. It may continue unchanged during the entire initial stage, and gradually or sometimes abruptly subside as the eruption appears. *Backache,* usually localized in the lumbar region, is a traditional and well-known symptom. This has special importance in the early diagnosis because it appears in no other acute febrile disease so frequently or with such alarming intensity. Sydenham compared this pain to that of kidney colic. It may be accompanied by pain in the thighs, hips, bones and joints, or extend over the sides of the chest and simulate the pain associated with herpes zoster or pleurisy. Pain and stiffness in the muscles of the back of the neck is common. The pain may occur with the early onset or appear in the last days of the initial stage, and usually disappears as the eruption makes its appearance.

Gastric disturbances are common during this stage, at the onset in the form of pain, nausea and vomiting, and later as anorexia and vomiting. So frequently is vomiting a symptom that some authorities state "no vomit, no smallpox." The tongue is usually covered with a whitish-yellow coat, and bears the marks of the teeth; the breath is offensive; injection and swelling of the tonsils and pharynx are frequent and pain in the throat is a common complaint. In cases with pharyngitis there is apt to be a more extensive eruption on the mucous membrane.

Menstruation appears almost regularly in the initial stage, even when the regular period has not arrived, and is usually abundant. This may be of importance in the early diagnosis. In pregnant women miscarriage is common at this period.

A more or less definite *chill* usually marks the onset. The temperature rises rapidly to about 104° F. and remains at this height with slight morning remissions for about three days. In the less severe cases the temperature falls to normal at the end of the third day; in the more severe, the decline is gradual, and the return to normal not completed until the fifth or sixth day. With the fall in temperature the eruption appears, the full development of which is reached after normal temperature is established. In a case of moderate severity the temperature usually reaches normal two days after the beginning of the eruption. The pulse and respiration are increased in proportion to the fever. The urine, at this time, usually contains albumin and presents the other characteristics common to febrile diseases. The *spleen* is frequently palpable and this

would be more commonly observed if carefully looked for. The nature of the disease tends to carelessness in complete physical examinations. The initial illness may be so severe that the patient may die before the appearance of the eruption (*variola siderans*).

Prodromal Rashes.—It has been only comparatively recently recognized that prodromal rashes occur in the initial stage of smallpox. It seems hardly possible that these interesting phenomena could have been entirely overlooked by the earlier observers but it seems even less likely that the character of the disease could have changed in this particular feature. The rashes were probably ascribed originally to mixed infection with measles or scarlet fever. The first description of a prodromal rash seems to have been given by Rembold in 1840. He says: "Cases are seen which have been regarded as a combination of smallpox with other diseases. I have observed cases of this sort at various times, and hold another view regarding them, namely, that they are not independent exanthemata appearing simultaneously with smallpox, but a condition of the skin which seems to introduce the smallpox eruption." The classical description of the prodromal rashes is by Simon, in 1870.

These rashes can be divided into three classes: (1) Erythematous; (2) petechial, and (3) mixed rashes. The *erythematous* rash usually appears on the second day of the illness, reaches its full development on the third day and disappears before the appearance of the specific eruption. The erythematous variety of rash may be scarlatiniform, morbilliform or multiform and may be seen as a general rash widespread on the body or it may be only seen in local areas. Such a rash may vary from a mere flushing of the face to a generalized rash which gives a bright red color to the entire body. The rash is, frequently, scarcely noted upon the extremities even when intense elsewhere, and it may be mottled, alternating with areas of normal skin. The rashes are seen most commonly upon the trunk and seldom upon the face. They are most noticeable in the inguinal region and about the axillæ. Although it is the rule that such rashes disappear with the beginning of the true rash of the disease, occasionally the prodromal rash persists even in the late vesicular stage.

The *frequency* of the prodromal rashes varies greatly but such rashes are never extremely common. Bancroft observed initial rashes in 16 of 1200 cases seen by him; Ker found that erythematous, petechial, or petechio-erythematous rashes were present in 14 per cent. of the cases seen by him, while Roger and Weil found prodromal rashes in 22 per cent. of the female and 14 per cent. of the male patients. As the prodromal rashes leave no staining behind it is difficult to estimate what percentage of smallpox patients would exhibit prodromal rashes if they were under careful observation from the beginning. The scarlatiniform variety of rash is the most common and has the appearance of a typical rash of scarlet fever but the mucous membranes are not involved.

At first sight the *morbilliform* rash is a duplicate of the rash seen in measles. Close observation reveals the macules to be larger than those of measles and these lesions remain macular instead of progressing to the papular stage as in measles.

There is an *erythematous* rash encountered in hemorrhagic cases that is so intense in color as to be termed a "lobster rash." This rash has an evil omen and is generalized all over the body and invades the face. It is early followed by hemorrhages into the conjunctivæ, and later over the surface of the body. As a patient so affected has not the slightest resemblance to typical smallpox infection, inexperienced physicians may not recognize the true nature of the disorder until other patients develop typical variolous rashes.

Petechial prodromal rashes are common and attract more attention, as a rule, than the erythematous rashes because they stain the skin. Such rashes may occur alone or in conjunction with the erythemas. Petechial rashes appear in different forms. Sometimes one finds small punctate spots, bright red or purple in color and scattered about on the body or appearing as diffuse dark blotches which only pressure discloses as made up of petechiæ. Bancroft noted that petechiæ were likely to be found in scar tissue, particularly in the lineæ albicantes of the abdomen. Petechial rashes endure longer than the erythematous flushings. The appearance of the petechial rash changes markedly after the third day, when the associated erythema usually disappears and the petechiæ become yellowish-brown and, at the end of the week, generally disappear.

The favorite seat of the petechial eruption is the lower abdominal region, with the genitals and the inner aspect of the thighs. With the patient on the back and the legs in contact, the affected area takes the form of a triangle, the apex of which is toward the pubes and the base crosses the abdomen transversely a little below the umbilicus. This arrangement of the rash has caused the name "bathing-trunk rash," as when it is seen from the front, it includes the region covered by the drawers of a bathing suit. The rash may also extend up the lateral surface of the trunk to the axilla, and from this point it frequently invades the axillary folds, the contiguous portions of the arm and the area of the pectoralis major muscle. This distribution of the rash is frequently spoken of as the "brachial triangle of Simon."

The prodromal rashes, other than the variety in hemorrhagic cases, have no prognostic significance. The occurrence of mixed rashes (erythematous and petechial) at the same time is not unusual. Different epidemics vary greatly in the number of patients exhibiting prodromal rashes.

The end of the initial stage, whether accompanied by a prodromal rash or not is marked by a decline of temperature, which may reach normal, and a general abatement of all the symptoms. The intellect becomes clear, sleep is restored, the headache and pain in the back cease, and the patient may possess a good appetite and normal digestion. This is an unusual feature in any severe illness and it seems characteristic of smallpox.

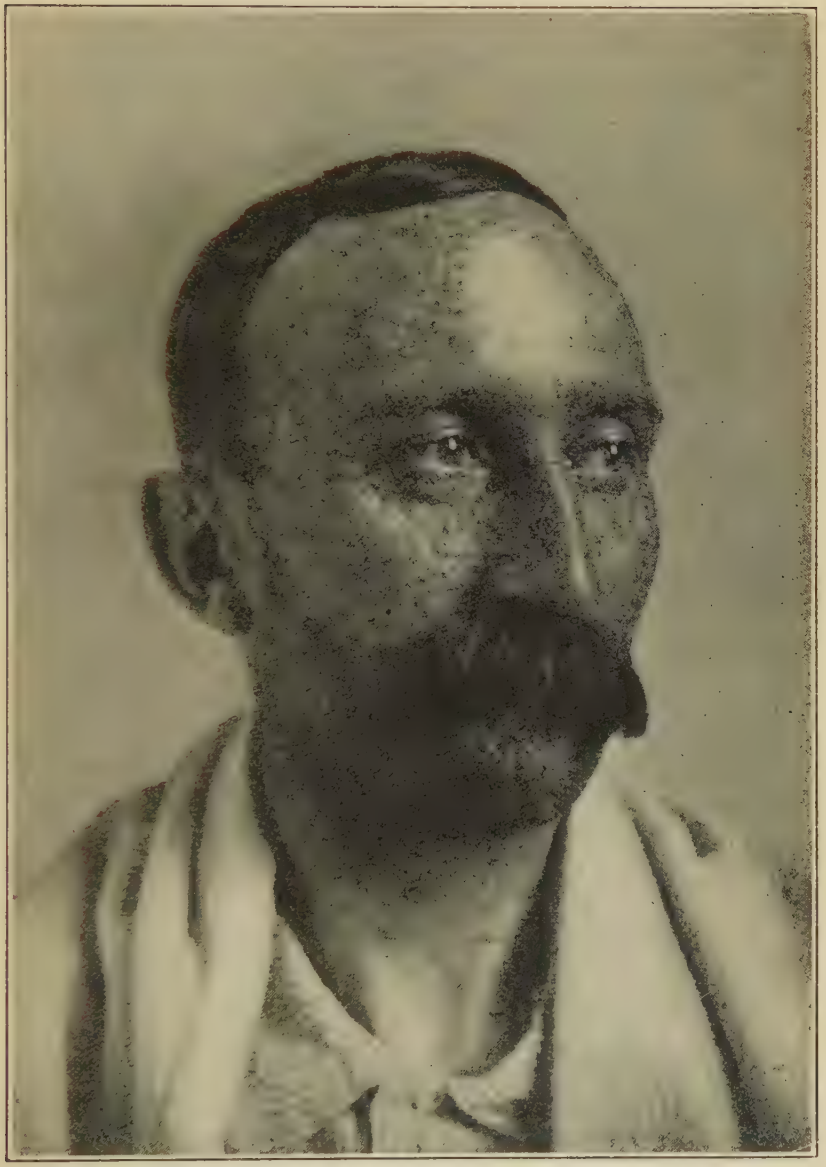
Eruption.—This is preceded by a diffuse erythema most marked on the forehead. The eruption varies widely according to the part of the body involved and the thickness of the skin. Patients ordinarily notice

the rash first upon the forehead and wrists. Close examination may reveal a few macules on the abdomen before the forehead and wrists are affected. The lesion first appears as a small red *macule* 1 to 3 mm. in diameter which in the beginning is slightly indurated. It becomes pale on pressure; on removal of the pressure the blood quickly returns. A capillary pulse is often noted in the macule and is seen most readily immediately after the pressure is removed. Within the middle of the macule there appears a small gray spot which gradually becomes filled with fluid. It increases in size, chiefly at the periphery, so that the periphery rises above the level of the centre, producing a crater or umbilication. The lesion becomes a tense hemispherical elevation, generally umbilicated, though it may be rounded, contains a gray transparent fluid, and is surrounded by a red areola.

The pock gradually assumes a yellowish tinge, and by the eighth day of the disease it is filled with a distinctly puriform fluid. It is not possible to empty either the vesicle or the beginning pustule by a single puncture. The fluid is contained in a number of cavities within the epidermis, and these do not communicate until a very late stage of pustulation. Close examination of the beginning vesicle, using a magnifying glass in bright light, shows that it is composed of a number of very minute clear points which correspond to the single collections of fluid in the epidermis. From the climax of development shown by the large, tense umbilicated pustule, a gradual retrocession, beginning usually on the tenth day, takes place. The lesion becomes less tense, its fluid contents disappear, and it becomes converted into solid reddish-brown material. This for a time is closely adherent, but later separates and falls off as a flat, hard, circular disk of an average diameter of 3 mm. In the beginning the macule is usually slightly indurated, and with the increase of the exudation within the epidermis the induration increases. In both vesicles and pustules the induration is marked; it is distinctly circumscribed, and gives the impression of a shot beneath the fingers. The development of the pock is accompanied by œdema of the corium and subcutaneous tissues. This is most marked on the face and eyelids, often causing complete closure of the eyes. The swollen countenance covered with brownish-yellow crusts, the closed eyes, the thick protruding lips dribbling saliva, and the uplifted hands, give a terrifying aspect to the patient.

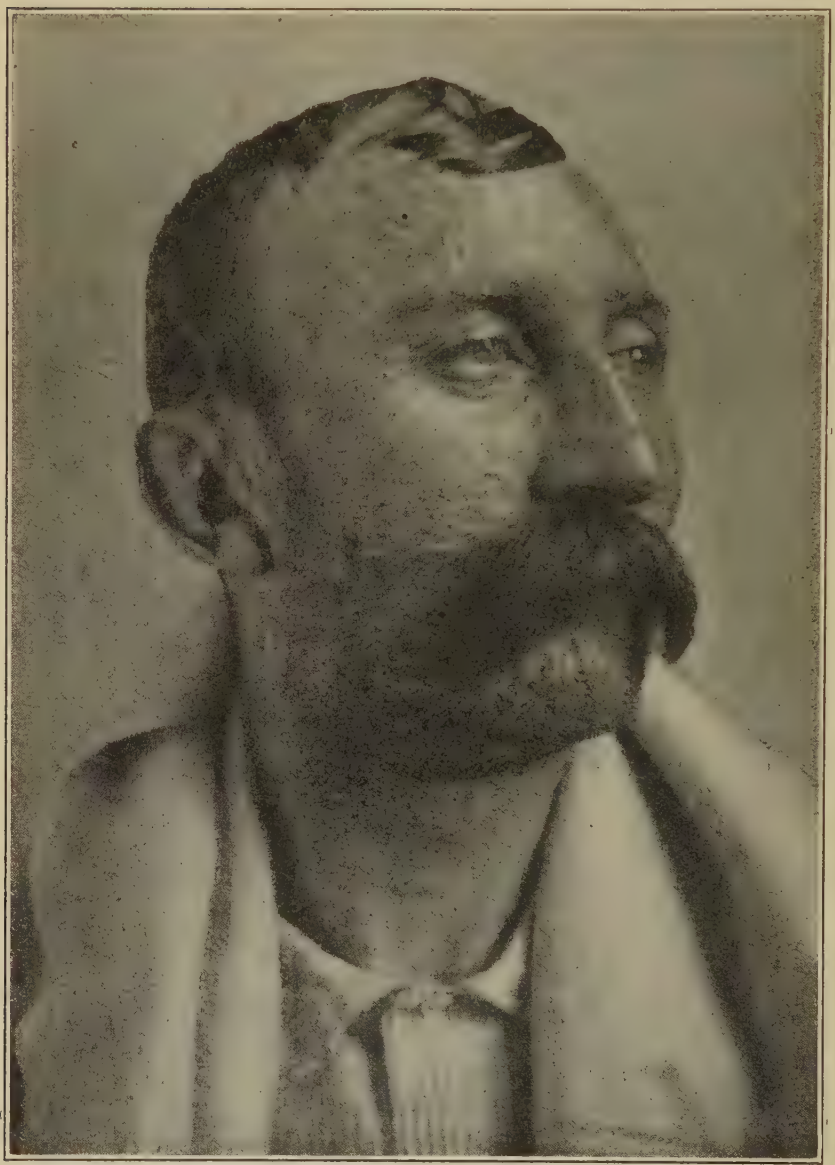
In the lesions on the *face* the initial induration is more marked than elsewhere. The early lesion of the face is a papule often with a shallow depression at its apex. The evolution of the lesion is here more rapid than elsewhere, and the pustular stage more quickly reached, the climax of development occurring on the eighth or the ninth day. By the ninth day, in all but the lighter cases, an exudate appears upon the surface of the pock, consisting of a thick, yellowish material which soon dries into a gray or greenish-gray crust. When the lesions are close together this may completely envelop the face and harden into a tough brown mark. When the pocks are separated, the exudate in drying forms a disk upon the apex of the pock. Upon the scalp the lesions appear later than they do upon the face and may cause great pain.

FIG. 2



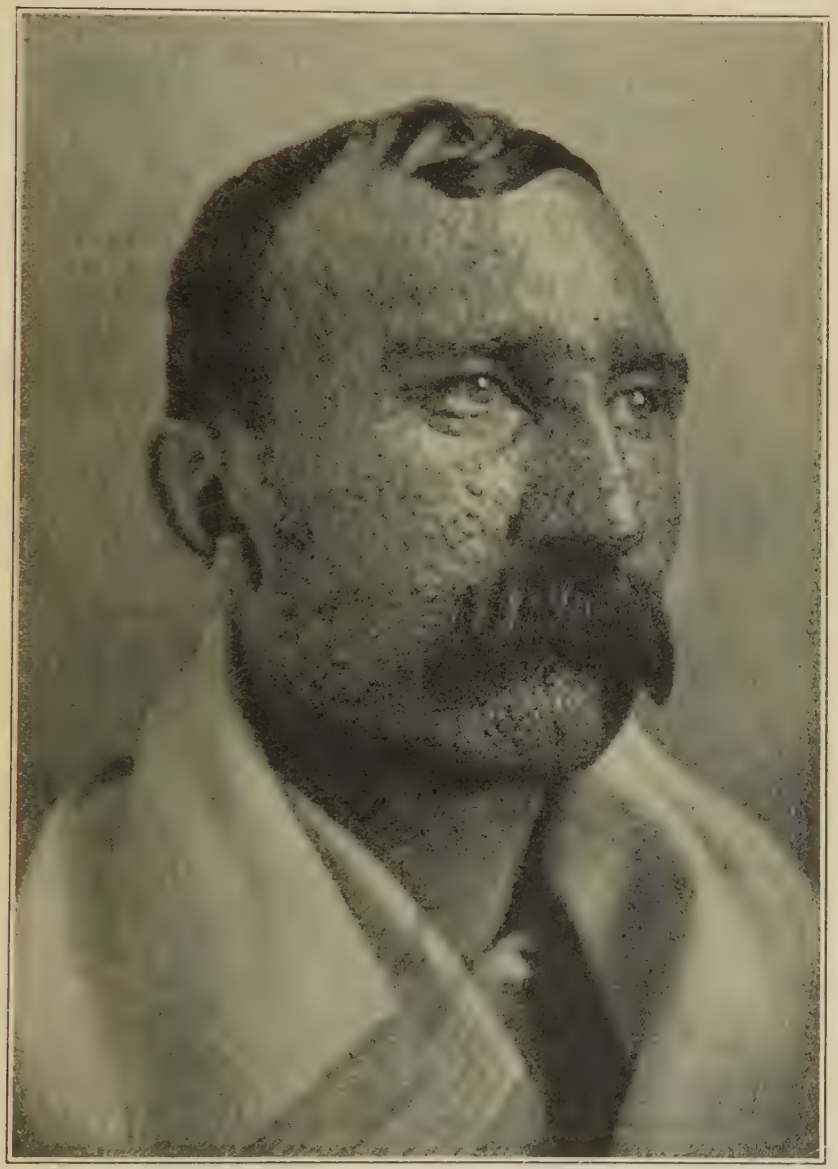
Serial photographs of smallpox in an unvaccinated man. Third day of eruption. (Welch and Schamberg.)

FIG. 3



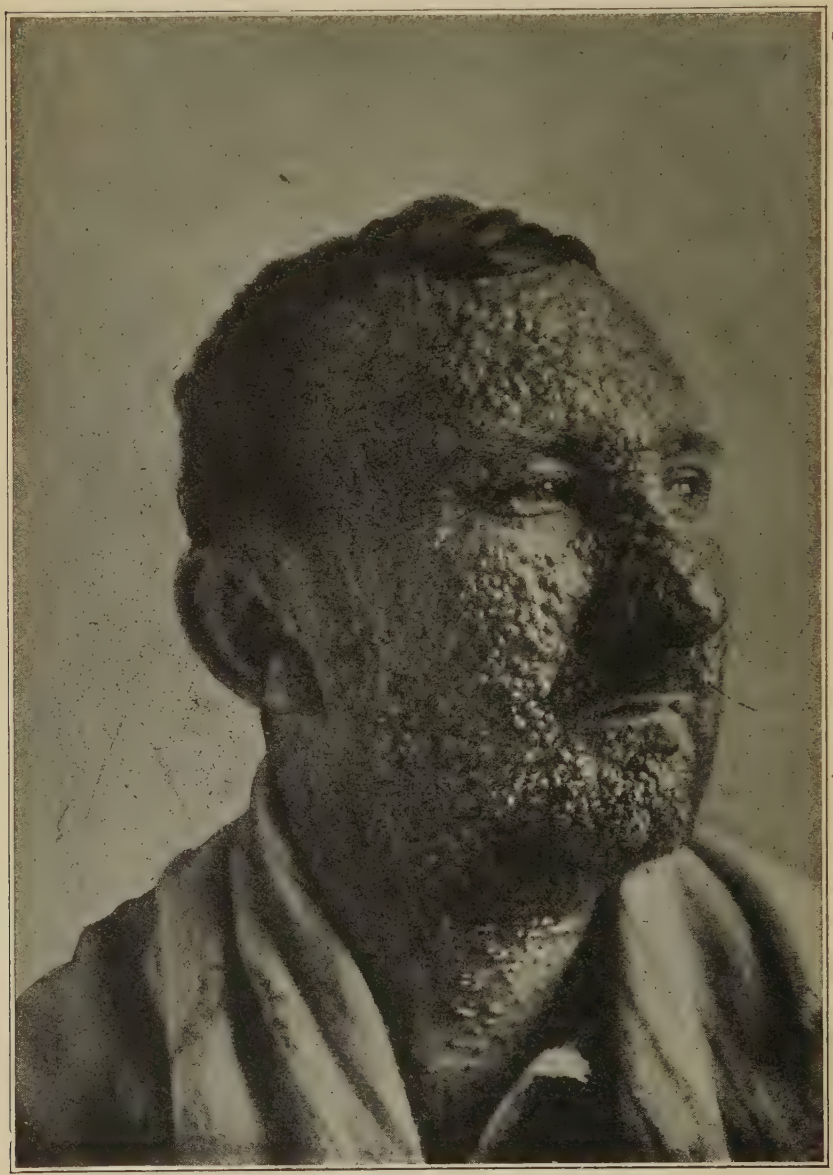
Fourth day of eruption. (Welch and Schamberg.)

Fig. 4



Sixth day of eruption. (Welch and Schamberg.)

FIG. 5

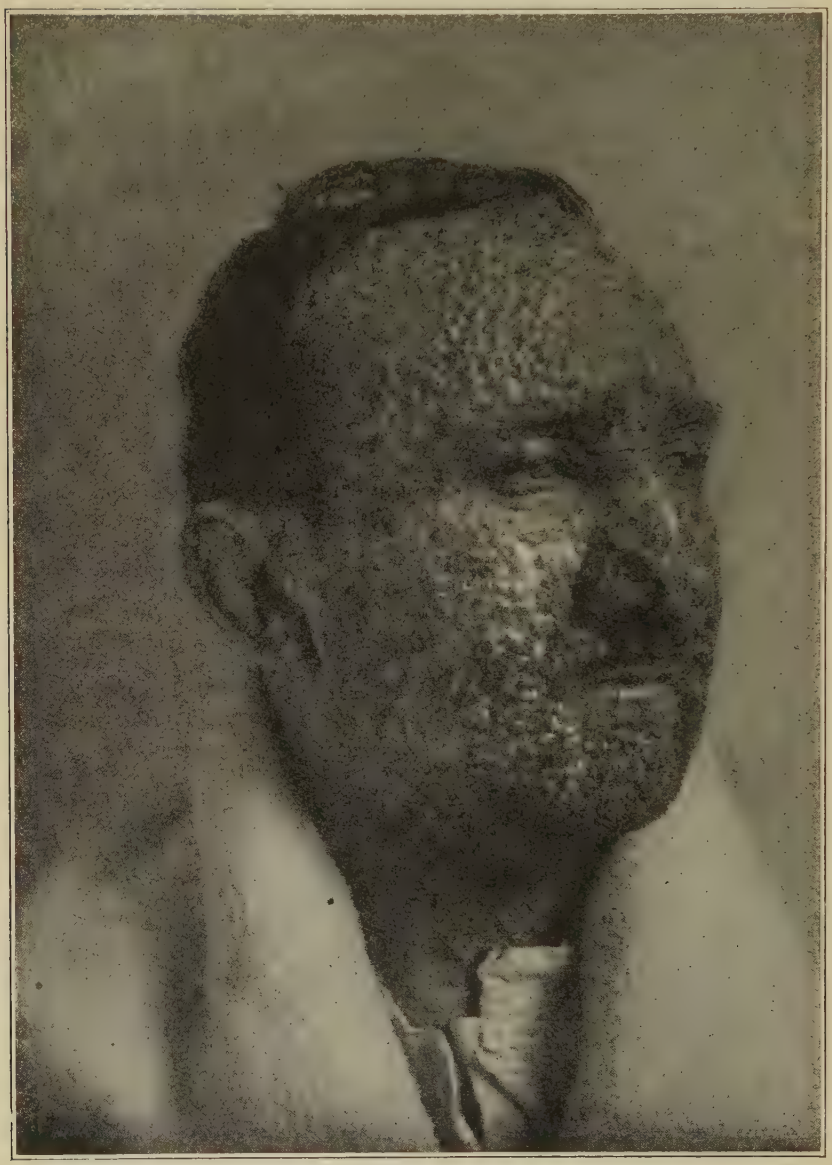


Eighth day of eruption. (Welch and Schamberg.)

FIG. 6

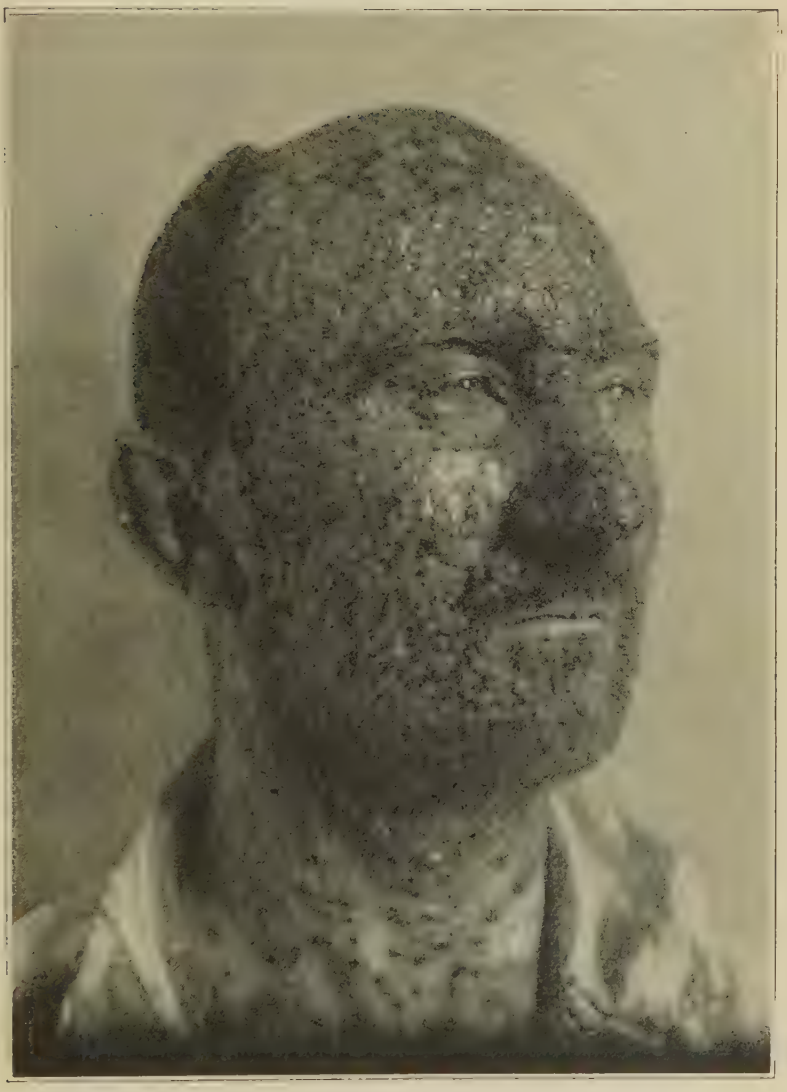
Tenth day of eruption. (Welch and Schamberg.)

FIG. 7



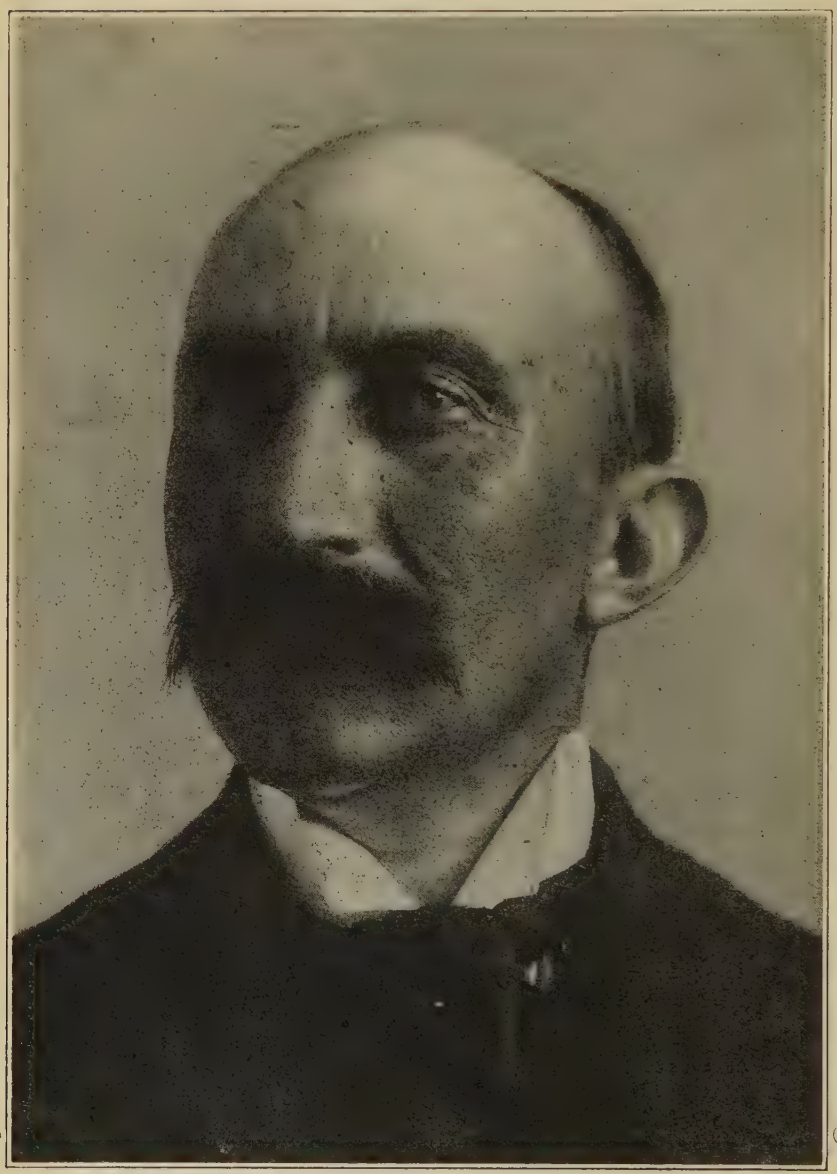
Twelfth day of eruption. (Welch and Schamberg.)

FIG. 8



Sixteenth day of eruption. (Welch and Schamberg.)

FIG. 9



After recovery. Scarring present, but not deep. (Welch and Schamberg.)

Upon the *hands* the eruption is abundant, and the tension produced by the pocks and the accompanying œdema cause great pain. The pain is intense when the pocks develop beneath the nail. The patient usually assumes a characteristic attitude, elevating both hands, and spreading the fingers as widely as possible. When the horny layer of the epidermis of the hands is thick, the pock may pass through all of its phases without distinctly elevating the surface. After the absorption of the fluid of the pustule, large disks remain beneath the horny layer, which must be picked out before the patient is discharged.

The eruption on the *trunk* is later in appearing than on the face or on the arms. It is usually less abundant on the abdomen and in the groins than elsewhere. It is profuse on the back, especially in its upper part, and here the lesions are generally accompanied by an extensive area of erythema surrounding the areola, forming irregular rectangular areas, the long axes of which are parallel with the ribs. This erythema persists until the pustular stage is reached. In general the lower extremities show the eruption later than any other part, although a small area of pock formation may appear very early upon the inner aspect of the thigh. The leg from the ankle to the knee is often almost wholly free.

The lesions on the face dry first; next, those on the arms; later, those on the trunk and the lower extremities. In children, owing to the thinness of the epidermis permitting the fluid of the pock to come through, and owing to the greater tendency to injury, crust formation is more common than in the adult. The crusts of the individual lesions fall off, and sometimes the epidermis of the palm or the sole is cast off in one piece, carrying the disks upon its inner surface. Scars result when the lesions are sufficiently deep to destroy the papillæ. The extent and character of the cicatrix depend upon the depth of the lesion. In studying the healing lesions in every stage Councilman never found any regeneration of the papillæ. In severe cases the nails fall off, and in nearly all cases the hair is lost during convalescence.

The eruption on the *mucous membranes* is typified by that on the soft palate. It begins here, often before the appearance of any lesions upon the skin, with the formation of a papule which develops into a vesicle which ruptures, forming a deep white erosion. The rupture takes place so early that it is exceptional to find unruptured lesions at autopsy. The eruption is most abundant upon the soft palate, although the entire mucous membrane of the fauces may be affected.

The pocks may develop atypically. One of the most common variations in severe cases is delay in the evolution, whereby the pocks, which in lighter cases are well filled out and pustular by the eighth day, do not reach their full development before the twelfth day. Another atypical condition is seen occasionally toward a fatal termination. Instead of developing into full, rounded pustules, the pocks may remain umbilicated, or even flatten down, puckering in the centre, and presenting a dull gray color. Not infrequently, and in cases which do not belong to the hemorrhagic type, the centre of the pock becomes dark red from hemorrhage. This is most frequent in the lesions of the forearms and legs. In certain cases the development of small vesicles is seen, which

have nothing to do with the pock formation, but are due to the elevation of the entire epidermis by œdematous fluid coming through. They vary in size from small foci, no larger than the beginning small pock vesicle, to large bullæ. They may be filled with clear fluid or the fluid may be dark from admixture with blood. The bullæ may occur in the midst of pustules, in which case these are elevated or split horizontally. Similar vesicles may be seen on the mucous membranes.

Any condition which gives rise to irritation of the skin influences the eruption, probably by causing increased vascularity. The eruption is often peculiarly abundant on the neck, where the collar is worn; along the line of pressure at the waist; and, in women, where the garter is worn. In a musician there was an abundant eruption on the shoulder where the body of the violin rested. There have been many observations of an abundant eruption in areas of hyperemia produced by a mustard plaster or iodine. An area of abrasion of the skin produced during the stage of incubation was surrounded by groups of pustules. On the other hand, one patient came into the hospital with an antiseptic dressing around the foot and lower leg which was allowed to remain. There was a very abundant eruption elsewhere on the body, and a total absence of eruption in the area beneath the bandage.

According to the character of the eruption, smallpox has been divided into a number of varieties. Such a division is artificial and the varieties merge into one another by intermediate forms. The typical cases of each variety are, however, fairly distinctive.

Smallpox Without Eruption.—This is the *febris variolosa* of Sydenham. In every extensive epidemic instances of this unusual form of the disease are seen. There is illness of an indefinite character, occurring chiefly in nurses, physicians, and hospital attendants, who are rendered practically immune by their former vaccinations, on the twelfth day after exposure to smallpox. The *symptoms* are headache, pain in the back, slight fever, gastric distress, and nausea. These may be so slight that the individual keeps at work, or they may approach in severity an ordinary initial stage. The symptoms last two or three days and then suddenly abate. Numerous examples were seen at the Municipal Hospital of Philadelphia during the epidemic of 1901 to 1904, when a large number of volunteer nurses and physicians went to the smallpox wards to assist in caring for the unusual number of patients. In several cases the symptoms were severe enough to confine the patient to bed and in at least two instances an eruption was expected because of the severity of what was thought to be "the initial stage." Characteristic initial rashes may appear during the attack. One patient, a pregnant woman, remembered having a headache about two weeks after exposure to the disease, but was not otherwise affected. Her child showed a typical eruption when two days old.

Abortive Smallpox.—There is properly a distinction between this and the mild form, but the term is often used to designate both conditions. It includes those cases in which the lesions are numerous in the beginning, appear to be following the usual course, and suddenly abate. The initial stage may be mild or most severe, accompanied by

delirium and unconsciousness, and continue for four or five days. The lesions may be smaller and more superficial than usual. The vesicle develops on the apex of the papule, never completely replacing it, and on the fifth and sixth days, instead of becoming a full, tense pustule, collapses and dries, forming a thin brown crust which is soon desquamated. Such cases of abortive smallpox have been confounded with varicella. This modification of the ordinary eruption is seldom manifested by all the pocks; more commonly certain lesions continue to develop into fully formed pustules, so that scattered among the abortive pocks are occasional typical pustules. The lesions of the lower extremities show the least tendency to modification.

Discrete Smallpox. This is the ordinary form, and includes all cases in which the lesions are not sufficiently numerous as to be confluent. Attacks in which the lesions are everywhere discrete usually follow a mild course. In 54 autopsies no cases with well-developed pustules were found in which there was not some confluence. The cases without confluence are those which die in an early stage before the eruption is fully developed, or those in which the eruption followed an atypical course.

Confluent Smallpox.—In this the eruption is so abundant that the lesions do not develop independently but merge into one another. Pustules may be very closely set and be seemingly confluent when they are not really so, the single lesions being separated by short intervals. Confluence occurs during the early active period of the development. From histological study it is evident that the development does not take place diffusely over a large area of the skin, but from single foci which in their development coalesce with those immediately adjoining. The confluence takes place in those parts where the eruption is usually the most abundant, most frequently on the face. The confluence may be apparent at the end of the first week. It is seen, next to the face, most frequently on the ankles, the dorsum of the foot, the hands, and the arms. In very severe eruptions the lesions may be confluent almost everywhere save on the trunk. The confluence undoubtedly signifies a more severe type of the disease. There is nothing in the confluence *per se*, it merely denotes a more abundant eruption and complete development. Sydenham called attention to the importance of the abundance of the eruption on the face in denoting the severity of the attack. It is rare to find typical confluent smallpox in an individual who has been vaccinated. In the old epidemics the majority of the cases often followed this type.

Hemorrhagic Pustular Smallpox.—A tendency to hemorrhage in, and in the vicinity of, the pocks always denotes a grave form of the disease. The eruption in these cases is abundant, but fully developed pustules are not numerous. The contents of the pocks may be hemorrhagic, but the tendency to hemorrhage is best marked by petechiæ in the skin around them. Such petechiæ are seen chiefly on the face, legs, and arms. Small vesicles may be seen on the surface of the petechiæ. Bullæ with hemorrhagic contents are also found. Sydenham described these and recognized their importance in prognosis. He describes them appearing upon "a ground covered with innumerable pustules, conspicuous in size, and filled

with a clear serum. When the vesicles were broken the skin underneath was black, and, as it were, mortified. Death was the lot of all those whom I ever saw with this fatal symptom." Such hemorrhagic cases seem to occur by preference in drunkards and in individuals weakened by antecedent disease. The tendency to hemorrhage is not confined to the skin, and there may be hemorrhages in the mucous membranes. Hematuria in this and purpuric smallpox may result from hemorrhage in the pelvis of the kidney.

Purpuric Smallpox.—This is the most atypical and fatal form, and it is doubtful if a well-marked case ever recovers. It is doubtful if a sporadic case would be correctly diagnosed, particularly if the physician was unacquainted with smallpox. It departs so much from the ordinary type that its status as a definite form of smallpox was not established until the German epidemic of 1870. It is most common during an epidemic, but can also appear sporadically. The frequency varies. In the epidemic of 1901 to 1902 Bancroft found 12 cases in 1200. It is generally held that it occurs most frequently in young and robust individuals, in men more often than in women. In Bancroft's 12 cases recent vaccination had not been practised in any, although unsuccessful attempts had been made in 2 within the two weeks preceding the onset of the disease; primary vaccination in childhood had been attempted in 7, of whom only 3, men of an average age of twenty-seven years, showed typical foveated scars; 3 were unvaccinated. The average age was thirty-four years. The *onset* is usually stormy, with chill, nausea, vomiting, and intense headache. This is not necessarily the case; 2 of Bancroft's patients worked during the first two days of the initial stage. The fever at onset is, as a rule, not so high as in ordinary cases. Usually on the second day a superficial bright red erythema appears, first on the chest, arms and face. Within twenty-four hours this may spread over nearly the entire body, and is accompanied by marked increase in the constitutional disturbances. Severe deep-seated and agonizing pain is felt in many parts, including the bones and joints, but is most intense in the precordium and epigastrium. The erythema changes from a bright red to a dark terra-cotta color. *Petechial ecchymoses* appear in it and may present little contrast with the general dark color. In extreme cases the entire body takes a general dark plum color, on which the petechiæ and ecchymoses may be faintly seen. There is great œdema, especially of the face. The mucous membranes, show the same tendency to hemorrhage. There is bleeding from the nose, and the nostrils may be partly occluded by the crusts of dried blood. Bloody saliva, due to hemorrhage from the gums, trickles from the mouth; there is a cough with bloody expectoration. The tongue, though swollen and coated, does not show the same tendency to hemorrhage as the other mucous surfaces. Women have abundant metrorrhagia, and abort if they are pregnant. The urine is scanty, albuminous, bloody, and contains blood-casts. The pulse is high and proportionate to the fever. In many cases death takes place before the development of any eruption. In some cases a few superficial vesicles on the face or elsewhere may be seen. In a most typical case, the only evidence of the eruption was a few scattered vesicles around the ankles.

Individuals who live until the fifth or sixth day may show the beginning of a typical eruption. The sensorium is clear even toward the last; patients may be drowsy, but they can be easily aroused and answer questions intelligently.

The relation of this form to smallpox is no longer in doubt. It occurs only after exposure to the disease, and exposure to it may be followed by the typical disease. All doubt is set aside by histological examination of the skin. This shows everywhere the earliest lesions preceding the formation of macroscopic vesicles. The foci are so numerous that had the disease progressed the entire body would have been covered by a confluent pock. In all cases examined by Councilman, there was an intense streptococcus septicemia. There is no tendency for this form to propagate itself; it may arise from and give rise to the mildest forms of smallpox. Death takes place at an average of four or five days from the onset and life is rarely extended beyond the sixth day.

Fever.—The temperature curve in discrete smallpox is almost as characteristic as the eruption. There is a sharp rise at the onset, which is maintained with slight irregularities during the entire initial stage. It then falls, in some cases rapidly, in others by degrees, to the normal or a little above, and maintains this during the vesicular stage of the eruption. At the beginning of the stage of suppuration, at the end of the first week, there is another rise, not so sudden as at the onset, nor does it ordinarily reach the same degree. The fever is maintained through the stage of suppuration until the beginning of desiccation, when it again falls, in some cases rapidly, in others by degrees. There is much more irregularity in the second rise than in the onset. Fig. 10 shows a curve from a rather mild case of discrete smallpox.

There has been considerable discussion in regard to the cause of the fever. Pfeiffer regards the first rise as specific and denoting the primary infection of the blood with the organisms which have entered from the hypothetical protopustule. At this time the organisms are deposited in the skin, where a second crop of organisms is produced, which again enter the blood and give rise to the secondary fever. There is not much in favor of this view. The onset of smallpox denotes the sudden action of a toxin. Not only the fever but the whole train of phenomena, especially those in the nervous system, seem capable of explanation by this view only. The primary fever may be regarded as denoting not blood infection but immunity. At this time the organisms in the blood are destroyed and the toxin combined with them is set free. Those organisms responsible for the skin eruption have been brought to the skin before. This is in harmony with experimental evidence as to the time of immunity production and the infectiousness of the blood. No experimental study of the blood has been made during the stage of incubation. The blood is not infectious so far as can be determined experimentally during or after the initial stage. There is no warrant for the belief that the second rise is anything more than the fever of suppuration and due to absorption from the skin. Its curve is in no way specific, and the fever varies in degree with the severity of the pustulation. The secondary fever does not necessarily take place. Fig. 11 is from a case of mild smallpox with

high initial fever and sudden fall. The low temperature continued during the course of the slight eruption.

While the fall of the secondary fever is generally by lysis, there may be a sudden fall as in the primary fever. Fig. 12 shows a case in which the high secondary fever fell suddenly in two days from 106° to normal.

Fig. 10

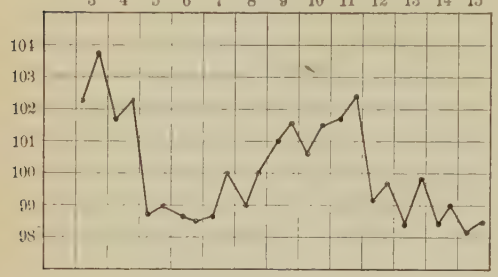


Fig. 11

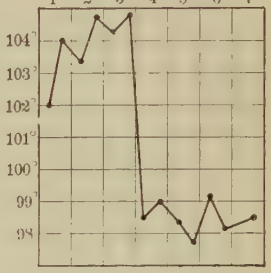
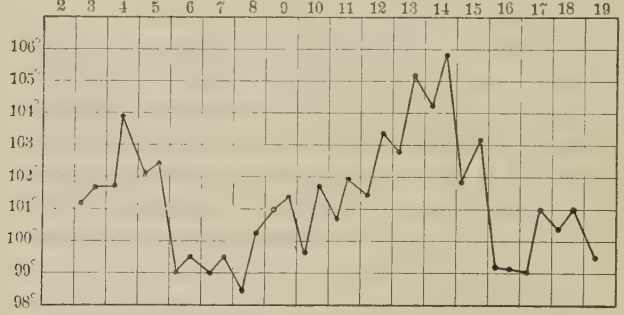


Fig. 13 shows a curve from a case in which there was a third rise coincident with the appearance of the secondary scarlatiniform rash and which terminated fatally on the twenty-ninth day. The secondary fever, being due to the suppuration in the skin and the absorption of the products from this, will be influenced by the varying conditions of the suppuration. Both the degree and the duration of the secondary fever are in proportion to the severity of the skin lesions. In slight cases it may not last more than three to six days, while in severe confluent cases it may last six to twelve days and may merge into the fever due to complications. In fatal cases there is often a high rise preceding death. In purpuric smallpox, the temperature neither in the onset nor in the course reaches the height observed in ordinary cases.

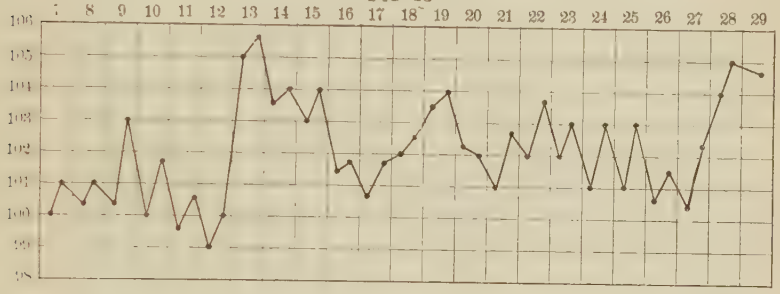
Fig. 12



The fever and the other phenomena of the suppurative stage denote toxic absorption. Delirium is common, not only in alcoholics, in whom the most violent forms are seen, but in other patients. This is also in great part dependent upon the severity of the eruption. Patients in delirium often strive to get out of bed and leave the hospital. In one instance a

patient, in the active suppuration of confluent smallpox, succeeded in leaving the hospital and wandered through deep snow to an ice-pound into which he waded. He was found after a few minutes, returned to bed, seemingly none the worse, and made a prompt recovery.

FIG 13



Urine.—Arnaud found albuminuria in 95 per cent. of his cases, the amount varying from day to day. Roger found albuminuria not as common. It was present in 15 per cent. of the mild, in 25 per cent. of the discrete, and in 28 per cent. of the confluent cases. Welch and Schamberg found albuminuria in 84.47 per cent. of the fatal cases and in 50 per cent. of the cases that recovered. In over half of the cases in which it was present it was discovered on or before the fifth day of the eruption. Casts were found more frequently in fatal cases than in those which recovered. They also found, as did Arnaud, that there was great irregularity in the character and constituents of the urine which may contain albumin and casts for several consecutive days, then perhaps on alternate days, then be free for a week or more, with a return to the pathological picture a few days later.

From Councilman's careful histological examination of the kidneys, there was nothing to indicate any special influence exerted upon them by the disease other than that due to the cytological blood changes. The degenerative changes were such as usually accompany acute febrile diseases associated with a varying degree of albuminuria. Acute nephritis occurs, as a rule, late in the disease and is to be regarded as a complication.

Blood.—There are certain rather characteristic changes and the examination, at certain periods, may assist in the diagnosis. The total number of the leukocytes is subnormal during the first five days of the disease, ranging from 4000 to 6000. After the fourth or fifth day leukocytosis occurs and from the ninth to the fourteenth day an average leukocyte count would be 17,000 although the leukocytes may be from 30,000 to 40,000. The polynuclear cells decrease in the first week, being 20 to 30 per cent. and later reach only 40 per cent. There is a decided increase in the lymphocytes. The first week there are usually about 45 per cent. and in the third week 65 per cent. Myelocytes are nearly always present in the severe forms and frequently in the mild forms as well.

Mild Smallpox.—From the oldest writers we learn that in early days, as now, there was great variability in the severity of different epidemics. Especially do they mention the unexplained and extraordinary mildness

of certain epidemics. Welch and Schamberg quote Van Swieten (1759) as follows: "The primary fever is often little more than febricula and the pustules seldom exceed more than one or two hundred. The form is so mild that secondary fever is not manifested, convalescence coming on at the eighth day of the eruption." Sydenham (1771) described an epidemic of very mild smallpox and stated that "smallpox also has its peculiar kinds, which take one form during one series of years and another during another." Jenner was familiar with the mild forms of the disease. He wrote: "About seven years ago a species of smallpox spread through many of the towns and villages of this part of Gloucestershire. It was of so mild a nature that a fatal instance was scarcely heard of, and consequently so little dreaded by the lower orders of the community that they scrupled not to hold the same intercourse with each other as if no infectious disease had been present among them. I never saw or heard of an instance of its being confluent. The most accurate manner, perhaps, in which I can convey an idea of it is by saying that had fifty individuals been taken promiscuously and infected by exposure to this contagion they would have had as mild and light a disease as if they had been inoculated with variolous matter in the usual way. The harmless manner in which it showed itself could not arise from any peculiarity either in the season or the weather, for I watched its progress upward of a year without perceiving any variation in its general appearance. I consider it, then, as a variety of the smallpox." Such an epidemic prevailed in various parts of the United States and was commonly supposed to have been imported from Cuba. It was variously known as "Cuban, Philippine, or Texas itch." The disease was known to be infectious but was so mild that opinion was divided between its being chickenpox, a mild smallpox, or a new skin disease.

The mildness of such epidemics is best understood by a study of the mortality. In 1901 there were in the United States 38,506 cases of smallpox and 689 deaths (1.79 per cent.); in 1902, 55,857 cases, with 1892 deaths (3.31 per cent.); in 1909, 24,099 cases with 150 deaths (0.6 per cent.); in 1910, 30,352 cases and 415 deaths (1.3 per cent.); from 1910 to 1924 the epidemics have continued to be very mild but with an occasional severe outbreak as though to keep us reminded of the real danger inherent in the disease. To allow an unvaccinated or insufficiently protected generation to exist in any community is plainly courting disaster. From the Statistical Department of the Metropolitan Life Insurance Co. come the following statistics of recent experiences:

NUMBER OF CASES, DEATHS AND MORTALITY FROM SMALLPOX IN 678 UNITED STATES AND CANADIAN CITIES DURING THE FIRST SIX MONTHS OF 1924, 1923, 1922

	Cases.	Deaths.	Deaths per 100 cases.
1924	18,811	242	1.3
1923	7,170	58	0.8
1922	7,355	228	3.1

When dealing with the mild forms of smallpox it is well to remember that the eruption may consist of a very small number of lesions which

may attract little or no attention and because of the mildness of the constitutional symptoms and the inconspicuous character of the rash, errors in diagnosis frequently occur until a severe attack is observed or a death occurs. The initial period in such cases may be typical. The *symptoms* may be mild or severe. As a rule, there is a sudden remission of the symptoms with the appearance of a slight rash. Welch and Schamberg report an instance in which only a single pock appeared. The pocks are usually small and superficial, at times amounting to little more than red spots, and may be readily overlooked or their nature unsuspected. Inquiry of the patient with well-marked smallpox, often brings to light the fact that about two weeks previously another member of the household had been sick, who, upon examination, shows a few healed pocks. In these slight eruptions the pocks are apt to be most abundant on that part of the body must subject to the eruption in well-marked disease. Some pocks are usually found upon the forehead, which may heal without leaving any perceptible scar. Usually an individual with a slight eruption of this sort is able to follow his occupation, and unless the pocks are fairly numerous upon the face, the disease is likely to be entirely overlooked. The disease is frequently spread by these mild cases. The habit of calling such cases *varioloid* has done much evil. The character of the disease in a second patient is not at all influenced by the character of the attack from which the infection is derived. Cases of confluent and purpuric smallpox are just as apt to follow infection from these mild cases as from any other form.

In 1912 an extremely mild epidemic, at first mistaken for chickenpox, occurred in Carbondale, Pa. An interesting feature, other than the lack of virulence, was the large number of unvaccinated individuals attacked (96 of a total of 97 cases). There were no deaths. At the same period in a city not far distant there was an epidemic in which the mortality was 27 per cent. During the past few years much has been written concerning a very mild form of smallpox in tropical regions to which various names have been given. Alastrim, Amaas, Kaffir pox, Sanaga pox, Cuban itch and mild pox seem indistinguishable from each other or from the mild forms of smallpox encountered in the temperate zone. As the disease is prevented by vaccination with cowpox and as the symptoms and rash vary in severity as in smallpox, it seems best to treat the disorder with all the respect that the more severe forms of smallpox command.

Histologically these mild cases present no differences from the same lesions in the severe forms. Both the protoplasmic and the intranuclear forms of the cytoryctes are present in the same numbers and relations. Such cases are now comparatively rare except in vaccinated individuals, as is evident from the descriptions of the disease in the prevaccination period and in mild epidemics. The mild cases are certainly very much more prevalent toward the close of an epidemic than at any other time.

Fetal Smallpox.—This is comparatively rare, but undoubted. Infection may take place at any time after the fourth month. It may take place earlier and the fetus perishes and is expelled before signs of the disease are evident. The fetus apparently passes through the typical stages of the disease. It may pass through the entire disease *in utero*

and be born with the resulting cicatrices and possess immunity; or the eruption may appear a few days after birth, or be perfectly developed at birth. There have been cases apparently well substantitated in which the fetus contracted the disease without infection of the mother. Such cases can be explained only on the assumption that the disease in the mother was so mild as to be overlooked.

Some cases regarded as fetal infection are not true infections. One such case occurred in Councilman's autopsies. The mother died on the thirteenth day of the disease and showed an abundant, partly confluent pustular eruption which was crusting in places. The child was fully developed and well nourished. The skin of the neck, shoulders, arms, chest, and back, presented small closely set elevations, from pin-point to half a millimeter in diameter, with a transparent vesicular centre and a white opaque border. The lesions were largest and most marked upon the the backs of the hands. The general color of the skin was dull violet. The microscopic examination of the skin showed absence of true lesions. The vesicles were due to the elevation of the horny layer of the epidermis by an exudation. The testicles and bone-marrow showed the characteristic lesions. No cytoryctes were found in the lesions. The condition of the fetus was regarded as due not to a true infection, but to the action of toxic substances which developed in the mother.

Councilman examined the skin from two others, in which the lesions were typical and contained the parasites in the same relation as in the adult. There seems no doubt that the specific organisms can pass through the placenta. The character of the disease in the mother has no influence on the infection, though it has an influence on the life of the fetus. Infection of the fetus can take place as readily in a mild as in a severe infection of the mother. It does not take place synchronously with the maternal infection. It is not possible to accurately determine the date of the fetal infection, but it appears to be about two weeks after the maternal infection and to take place at about the period of onset. It is probable that at or just preceding the onset there is the greatest amount of infectious material in the blood of the mother. The general opinion is that the immunity acquired by the mother is not transmitted to the child. Vaccination of children whose mothers had passed through the disease in pregnancy has proved successful in the majority of cases. In some cases the infection of the infant has taken place at birth, the eruption appearing sixteen days afterward.

Complications and Sequels.—These are frequent, although none are peculiar to the disease but are such as we would expect to find in accordance with the character of the lesions. With the beginning of suppuration the specific character of the disease is over, but a suppurative process of great extent remains, usually with streptococci in the foci of suppuration. These foci offer favorable conditions for absorption and blood infection by the bacteria. Not only the skin but many of the mucous membranes are affected. No sharp line can be drawn between the complications and the sequels. We should expect to find complications due to the action of the specific toxic products of the disease. Most of these are included in the delirium and other symptoms of the initial

stage. It is probable that there are others which appear later in the disease, such as the specific orchitis.

Among the most common complications are *boils*. These appear most commonly after the stage of decrustation, about the third week, and add greatly to the suffering of the patient. They appear in crops and often have a very protracted course. It is unusual for a patient to pass through an attack of smallpox, unmodified by vaccination, without suffering from numerous furuncles. They are due in some cases to direct extension of the infection from the pustule, in others the infection takes place through the hair follicles from the surface. There may also be deep subcutaneous abscesses and diffuse spreading suppurations which cause a fatal termination. The entire skin of the leg, arm, or scalp may be undermined. Septicemia due to this infection is by no means uncommon. Erysipelas is rare when we consider the opportunities for infection. Welch and Schamberg noted but 10 cases in 2000 patients. When it does occur it usually comes on after the third week.

Complications affecting the *respiratory tract* are common. The extensive, deep, and destructive ulceration of the larynx, which sometimes occurs, is usually fatal. In other cases the laryngeal lesions may produce cicatrices and deformities. Lesions in the lung are so common that they may be regarded as symptoms rather than complications. They are more common in the severe than in light cases, and consist chiefly of bronchitis and bronchopneumonia due to streptococcus and pneumococcus infection. Lobar pneumonia is uncommon and is to be regarded as an accident and not related to the disease. In 54 autopsies it was found in 2 cases. Bronchopneumonia may be so extensive as to simulate lobar pneumonia. Pleuritis occurs occasionally but not nearly as often as one would naturally expect. Pleural effusion is less common than hydrothorax due to nephritis or a failing heart. Empyema is uncommon and usually due to infection of the pleura from the lung and not to metastasis.

The *heart* suffers the changes which attend any severe febrile affection. Myocarditis is a complication in a very large number of cases, particularly in the severe infections. Pericarditis and endocarditis are noted rarely. Phlebitis occasionally occurs during convalescence.

Chondritis, osteitis, and osteomyelitis are uncommon complications and are sometimes seen as sequels. Metastatic purulent arthritis occurs rarely and most often in children. The elbow is most frequently affected and next the wrist.

Deep and superficial necroses of the soft palate and the pharynx occur, not accompanied by membrane; glossitis is occasionally seen, and less frequently noma. Parotitis occurs in a few severe infections. Thyroiditis is seen especially in young girls at or shortly after puberty. Bed-sores are less frequent than one would expect. Gangrene of the skin, often of considerable extent, may develop during the suppurative period in severe cases. It is usually superficial and seems to be due to the stasis of intense congestion. Many cases of extensive gangrene are fatal.

Complications affecting the *eye* are common. In the prevaccination days, blindness was a common result of severe attacks. Pock formation,

though common on the lids, is uncommon on the conjunctivæ, though it undoubtedly occurs. The common conjunctivitis is due to infection with pyogenic bacteria combined with retention of secretion and circulatory disturbances due to tightly closed and swollen lids. The swelling of the lids is often so extreme that the eyes cannot be opened. Ectropion may result from contracture of the cicatrices of the lids, which follow the pocks. When blindness results it is due either to corneal ulcers, which may perforate, or to pock formation on the conjunctivæ at the edge of the cornea. Marsten in reviewing 15,000 cases of smallpox found but 26 in which the pustule had been seen upon the conjunctiva. A true pock formation on the cornea does not take place, which is one of the best evidences of the dissemination of the organisms by the blood-stream. Councilman saw a true pock form in a vascularized cornea, which did not differ from the common lesions on mucous membranes. The external ear may be the seat of pock formation and the swelling may completely close the external meatus. Otitis media is common and occurs most often in the convalescing wards particularly in children. In a few cases thrombosis of the cerebral sinuses has followed but mastoid inflammation and suppuration are rare.

Nephritis is not common, but albuminuria is common. Nephritis is usually a late complication. Suppurative nephritis is infrequently found. Cystitis is rare as a complication or sequel, but often occurs in very ill patients who do not empty the bladder completely. *Orchitis*, single or double, and usually accompanied by effusion into the tunica vaginalis, is rare and usually occurs during the pustular stage of severe attacks. Welch and Schamberg found it in 8 of 2000 cases.

The complications and sequelæ affecting the *nervous system* are numerous. An excellent account of them is given by Immerman. There is very little anatomical change found in the nervous system. Southard, after careful study of the cortex, found no lesions. Focal lesions, consisting of hemorrhage and inflammation, have been described in both the brain and cord. The sudden hemiplegia and more partial paralysis which occur rarely in the course are to be attributed to such focal lesions. Affections of the cord are more common than of the brain, the most frequent being motor paraplegias. These are not confined to severe cases but are nearly as common in mild attacks. They may appear in any stage and have been described as occurring in the stage of incubation. The paralyses occur suddenly; the bladder and rectum may be involved, but sensation in the affected area may remain. Cases have been described in which the paralysis assumed a rapid, ascending character, giving the clinical features of Landry's paralysis. Post-variola paralysis of the palate and pharynx has been described. It is unknown whether there was a mixed diphtheria infection in such cases.

Diagnosis.—This may be very easy or very difficult. It is not possible to make a diagnosis in the initial stage unless one has a definite history of exposure in an unvaccinated subject. Even the most typical onset and initial stage may be paralleled by other acute febrile diseases. The prevalence of an epidemic or the history of exposure will awaken suspicion in illnesses that, without such history, would be diagnosed influenza,

dengue or other acute illness. In the intervals between epidemics it is not likely that the most typical initial stage would suggest smallpox unless the physician has a personal and extensive knowledge of the disease. The prodromal rash is not sufficiently common to give much help and prodromal rashes occur in other acute exanthematous diseases. A petechial prodromal rash upon the abdomen below the umbilicus, and extending to the groins, on the second day after an acute onset, with chill, nausea, and headache, is most suggestive when it occurs.

The diagnosis nearly always can be made after the specific eruptions have appeared, even if the rash is scanty. There may be doubt between smallpox and *measles*. Apart from the history of preceding catarrhal symptoms and the presence of Koplik's spots in measles, both of which are absent in smallpox, and the different course of the fever, which in smallpox diminishes with the appearance of the eruption while in measles it increases, a careful examination of the eruption will decide. The eruption of smallpox, even though it may appear in the beginning to naked-eye examination to be papular, really is not so but is vesicular. The vesicular character is usually most evident where the skin is thinnest, particularly on the inner surface of the thighs and on the scrotum. The use of the magnifying glass in a good light is often of material assistance in determining the true character of the eruption. The apparent papules rapidly become vesicles, while the measles eruption remains papular. The eruption of measles has a velvety feel and shows a distinct tendency for the grouping of the lesions into crescentic patches. The eruption of measles covers the entire body and does not spare those parts, the flank for instance, which usually shows little rash in smallpox. The papules of measles, especially upon the brow and forearm, can be quite hard and "shotty" to the touch while in smallpox, especially if the attack is modified by vaccination, the lesions may be quite soft. If the temperature of the patient is lessening while the rash is increasing it is presumptive evidence that one is dealing with smallpox. In measles the temperature, as a rule, continues to rise after the true rash appears. A differential diagnosis made solely upon the appearance and feel of the eruption may easily be wrong. It must be based upon the vaccinal state of the patient, a carefully ascertained history of the early stages of the illness, a search for Koplik's spots, a minute examination of the eruption, a study of the temperature chart, when obtainable, and in difficult cases upon repeated examinations.

The greatest difficulty lies in differentiating atypical smallpox from equally atypical *chickenpox*. A number of the ancient medical writers believed in the unity of the two diseases because they encountered severe infections of chickenpox with aggravated features and extremely mild examples of smallpox with few and scattered lesions and practically no symptoms of illness. To make a correct differential diagnosis it is necessary to do more than merely to glance at the rash.

As in all differential diagnoses in which smallpox is to be considered the *vaccinal* condition of the patient is a most important factor. The initial symptoms are extremely important in the differential diagnosis because, although there are important exceptions, the rule is that in

chickenpox the eruption is the first manifestation. It is true that an attack of chickenpox may be associated with moderate or even high fever but this does not, as a rule, appear until the eruption is in evidence. At times comparatively severe symptoms occur in an attack of chickenpox, chills or chilly sensations, vomiting, headache and even convulsions but usually an examination of the patient's body will at that time reveal the rash of chickenpox. Both diseases are characterized by vesicular eruptions and in both the lesions are in the epidermis. When the lesions of chickenpox are completely formed they are more sharply elevated, rounder and more translucent than in smallpox. The fluid is contained not in a system of cells, as in smallpox, but in a single cavity that can usually be emptied by a needle prick. This is frequently a helpful test. In chickenpox the lesions develop much more rapidly than in smallpox, and appear in successive crops. The vesicles of chickenpox often remain with clear contents and do not, as frequently, change into definite pustules. The superficial character of the chickenpox lesion allows it to assume irregularities of shape which do not occur in the lesions of smallpox.

There is seldon the hard, shotty feel to the vesicle that one so frequently encounters in smallpox but in certain areas, notably on the forehead, the lesions of chickenpox may closely resemble the feel of smallpox vesicles. In chickenpox the first vesicles are nearly always on the body, especially on the back, while smallpox lesions appear first, as a rule, on the hands and wrists. As pointed out by Ker, of Edinburgh, the comparative immunity of the forearm and hand from the eruption of chickenpox is an important differential point. The presence of many lesions on the flanks, if the lesions are otherwise scanty, favors the disease being chickenpox. Welch used to call attention to the fact that in chickenpox the lesions are found on those areas covered by clothing while in smallpox the exposed surfaces were more commonly and primarily affected. The chief difficulty lies in distinguishing between mild or abortive smallpox, in which the lesions tend to remain in the vesicular stage, and severe forms of chickenpox. These abortive and mild cases of smallpox may have a very mild and almost unnoticed onset and initial stage, and no more constitutional disturbance during the eruption than in chickenpox. In such cases a close study of all the features of the eruption with a survey of the history will usually decide. The course of the eruption is often very revealing for even in the atypical cases of smallpox there is not usually so sudden and complete drying of the vesicles as in chickenpox, and the scab from a smallpox lesion is always firmer and more elastic than in chickenpox, which produces a granular, easily disintegrated scab. It is frequently wise to vaccinate a suspected chickenpox suspect as an aid in the differential diagnosis.

Confusion sometimes arises between the lesions of pustular *syphilis* and atypical smallpox. The diagnosis may be difficult when the pustular syphilide is well-marked and the lesions of smallpox few and atypical. Syphilitic eruptions may be accompanied by fever and other constitutional manifestations but the presence of enlarged inguinal, post cervical and epitrochlear glands and the presence of mucous patches in the mouth frequently aid in a differential diagnosis. Occasionally a Wassermann test is necessary.

The vaccinal condition, the medical and venereal history, past and present, a careful study and sometimes more than one careful study of the lesions will prove sufficient.

Some observers have found difficulty in distinguishing between the lesions of smallpox, *pemphigus* and *impetigo contagiosa*. In pemphigus the lesions vary greatly in size; there is little induration at the base, the covering of the skin is formed by the horny layer alone and is much thinner. In smallpox in the vesicular stage, while the majority of the lesions might resemble pemphigus, certain lesions will almost certainly be found in the papular and others in the vesicular and pustular stage. In impetigo contagiosa a close examination with section into the lesion should decide and the same method will exclude *molluscum contagiosum* These lesions vary greatly in size and extent and the lesion is in the corium and not in the epidermis.

Drug eruptions, particularly those caused by the salts of bromine and iodine, closely resemble the lesions of smallpox at times. The absence of constitutional symptoms, the irregular development of the rash, and the history of taking drugs, aid in clearing the diagnosis. *Herpes* and *acne* have rarely caused difficulty in the diagnosis except when the patient also has an acute illness, like pneumonia, that has not been suspected. The distribution and appearance of the lesions will seldom lead one astray.

The difficulty in diagnosis between *acute pustular glanders* and smallpox seldom arises. This form of glanders is unusual, and generally occurs in those whose occupations bring them into contact with diseased animals. In glanders abundant pustules may appear in the skin and superficially simulate a variolous eruption. The patient with glanders is sicker than he would be with a corresponding smallpox eruption. The pustule of glanders is a true abscess of the corium, and the epidermis has no part in its formation. It arises as an abscess, is not so circumscribed as is the smallpox pustule, and beneath the finger feels more distant.

While the history and the fever may make one very suspicious of the diagnosis of smallpox only the appearance of the eruption is decisive and then only for one who is familiar with the disease. There is a laboratory method (Paul's) which involves the inoculation of the cornea of a rabbit with the contents of a smallpox pustule or vesicle. In forty-eight hours there is slight opacity at the point of inoculation, and on microscopic examination swelling and proliferation of the corneal epithelium, with numerous cell inclusions, is found. A more rapid and equally certain method is concerned with the direct examination of the contents of a vesicle or pustule by the microscope. No other pathological process gives the same histological picture as the smallpox lesion and no other shows in the cells the characteristic parasite inclusions (Councilman).

Prognosis.—This is chiefly influenced by five factors:

(1) The vaccinal condition of the infected patient. (2) The age and state of general health of the patient. (3) The severity of the particular epidemic during which the patient is ill. (4) The type of the disease and the accompanying complications and sequels. (5) The amount and quality of nursing and medical attention received. By far the most

important factor is the vaccinal condition, for not only is infection in vaccinated individuals comparatively uncommon, but the severe types of the disease are less frequent and the mortality much lower. The next most important factor is the character of the epidemic whether mild or severe.

The *age* of the patient is of great importance. It is unusual for an unvaccinated infant to survive an attack of confluent smallpox, although in epidemics of a very mild character the mortality may be extremely low, even in infants. The mortality in children of the pre-school age is high because so few of them have been vaccinated. In the period from five to fifteen years the prognosis is better than in adult life because the children have, in the majority of instances, been successfully vaccinated to comply with the requirements of the school health codes. The mortality in patients over fifty years of age is always high except in very mild epidemics and in recently successfully vaccinated individuals. The mortality of unmodified smallpox after middle life is naturally higher than in adolescence, as the immunity due to childhood vaccination is frequently largely exhausted. Many patients after fifty have organic disease which influences the prognosis unfavorably. The general health of the patient is an important factor. Among women the mortality is increased because of their liability to suffer from uterine hemorrhages, or from miscarriage or premature delivery in any stage of pregnancy. The occurrence of miscarriage or premature delivery apparently predisposes to the hemorrhagic form of the disease. In patients addicted to alcohol the disease is likely to be severe and drunkards seem predisposed to the more severe forms. Chronic diseases of any kind add to the gravity of the malady. Especially does this apply to patients suffering from pulmonary tuberculosis, severe forms of myocarditis and chronic nephritis.

The *type* of the disease and the extent and depth of the eruption are the most important factors, apart from the vaccinal condition, in the prognosis. The character of the initial stage may effect the prognosis. A mild initial stage is indicative of a mild form of the disease. A severe initial stage may, however, be followed by a mild form. True hemorrhagic smallpox is practically always fatal. There is a modified form of hemorrhagic smallpox in which recovery sometimes occurs, but even in such cases the prognosis is not good.

Next in severity is the confluent variety, the mortality of which is always high. Of 211 cases of this form seen in the epidemic of 1871 and 1872, by Welch and Schamberg, 168 died, a mortality rate of 79.62 per cent. In modified smallpox the mortality depends upon the complications rather than upon the primary disease. The character of the epidemic markedly influences the mortality. The pandemic of 1901 and 1902 in the United States was characterized by a remarkably low death rate but there were striking local differences. In certain sections of the country the mortality was *nil*, while in others it was as high as among the unvaccinated in the old epidemics.

The decline in the mortality from the epidemics of the eighteenth century is due solely to vaccination and revaccination. Although there is evidence that the disease is growing milder there should be no careless-

ness regarding the necessity of primary vaccinations and systematic revaccinations for we can expect epidemics of the disease, severe in character, from time to time.

The prognosis is decidedly influenced by the type of the eruption and depends essentially upon its intensity and extent. Starting from smallpox without eruption and mild smallpox, in which there may be no fatal cases, there is a steady ascent to the cases of purpuric smallpox with a mortality of 100 per cent. The mortality of confluent smallpox is always high, averaging 60 per cent. It is not always possible to predict the character of the disease during the vesicular stage, for the eruption may be abundant, simulating the beginning of a confluent case; but the vesicles may dry, very few of them become pustular, and the fever and other phenomena of the pustular stage may be absent.

There is no evidence that *race* has any influence upon the prognosis. The disease has always been very virulent in aboriginal tribes; but in the unvaccinated everywhere the mortality may be high. In ordinary epidemics the mortality is high among the negroes; but these citizens are the most careless regarding the necessity for vaccination. The serious complications due to extensive streptococcus infections of the mucous membranes, with a possible septicemia following, are especially unfavorable. The prognosis in the individual case can be best determined by an accurate knowledge of the extent and character of the disease and the effect it is exerting upon the important functions. The most lethal period of the disease is in the second week, at the height of the suppuration, and chiefly between the ninth and twelfth days of the illness.

Prophylaxis.—Smallpox is a preventable disease. Its existence in any community is a reflection upon the intelligence of the citizens. If there existed uniform and proper laws for initial vaccination and systematic revaccination of the population and if such laws were vigorously enforced smallpox would soon be an extremely rare disease. Even with the existing laws and regulations if each practising physician visualized his opportunities or fully appreciated his responsibilities in connection with vaccination and revaccination of his own patients the civilized world would soon look upon a case of smallpox as a unique curiosity. As a profession, unfortunately, we physicians cannot but feel that we have failed in our duty when an epidemic of smallpox spreads through a community. In every community in which vaccination and systematic revaccination are not carried out the appearance of a sporadic case of smallpox or the importation of a case from some other locality may easily result in a more or less widespread epidemic.

We are probably correct in assuming that the infectious material exists in the eruption, that it may be carried through the air an unknown distance, that everything and everybody coming in contact with the patient may carry and retain dangerous material, and that this infectious material may, for a long time, retain its infective power.

The first step toward prophylaxis after a case of the disease is discovered is the prompt isolation of the infected person or persons and the equally prompt vaccination with potent virus of all individuals who have been exposed to the infection. In unusually favorable circumstances (which

are extremely rare) it may be practical and possible to properly isolate the patient and the attendants in a private house. Such a plan, however, has many and serious difficulties and proper isolation is best conducted in a well-managed isolation hospital, the staff of which is thoroughly familiar with the management of the disease. Contrary to lay opinion it is more necessary to isolate the patients with mild infections than to isolate those more severely ill of smallpox. The individuals suffering mildly from the disorder are frequently almost free of disabling symptoms and such patients frequently play an important role in the dissemination of the disease as they are entirely unconscious that they are a menace to the health of the susceptible.

As long as no unalterable policy exists for systematic vaccination and revaccination all large communities must provide for the isolation and proper care of smallpox patients. The most practical arrangement is to have a smallpox department in the hospital for infectious diseases. It should consist of simple, barrack-like structures isolated from other departments of the hospital. There should be a capacity for extension, during epidemics. As a rule the smallpox hospital is used only during an epidemic and is unprovided with laboratories and opportunities for investigations. The energies of the physicians in charge of the patients during an epidemic are usually entirely devoted to handling an unusual situation. Such a hospital should be used for teaching purposes, because its medical students and practising physicians should observe and study smallpox infection as any other disorder.

Provision should be made for the care and supervision of those individuals who have been exposed to infection. All exposed persons should be vaccinated as soon as possible. If vaccination be performed with potent virus immediately or soon after the exposure, the vaccine immunity will develop in time to protect from the disease. Vaccination may be successful up to the fourth day after exposure, but rarely after this but vaccination should always be performed even if its protective influence can hardly be expected. If performed too late to protect, both vaccinia and smallpox run their course independently. The attempts at vaccination of detention patients should be thorough and repeated if unsuccessful. The detention cases should be kept under close observation and any one developing symptoms should be isolated and treated as an infected individual.

If there is the least doubt as to the correct diagnosis on admission of a patient, he should be vaccinated with multiple vaccinations and isolated until all doubt of the diagnosis is removed. We do not know how long the infective principle lives in smallpox and in the absence of this knowledge it is safest to assume that it is as resistant as bacterial spores. All methods of disinfection should be so thorough as to destroy spores. Disinfection can be so thoroughly carried out that there is no necessity for the destruction of all articles which may have been infected. Nurses and others in constant attendance on infected patients should be isolated, as it is possible that those coming into the infected atmosphere may carry the infection to others. All persons coming in contact with the disease should either have a special entire suit of outer clothing or wear a suitable

gown and cover the hair with a cap. Overshoes should be worn and discarded immediately before leaving the infected atmosphere. An exposed person should carefully bathe the exposed surfaces of the body before coming in contact with non-immunes.

The smallpox patient should be detained until all the infected epidermis is removed. It is thought by some that the dried disks contain the infectious material although this has been denied by others. The remnants of the pocks remain longer when enclosed in the thick epidermis of the palms and soles than elsewhere, and their artificial removal (picking out the disks with the point of a knife) will assist in the cleaning process. The patient should then be scrubbed on more than one occasion and provided with uninfected clothing before being discharged. In the event of the smallpox patient having been isolated in a private home disinfection of the premises occupied by the patient is imperative. It is safest to remove the wall paper and to thoroughly clean the walls before these are repapered. All bedding and other fomites must be thoroughly disinfected.

Treatment.—There is no specific treatment. Efficient nursing is far more important than routine medicinal treatment although certain distressing symptoms can be alleviated and complications prevented by skilful medical care. With the great variation in the severity of the disease in different epidemics, it is easy to understand how methods of general and local treatment have arisen, been advocated and used for a time and then supplanted by other methods. In the treatment of many diseases a nurse is a luxury, but in smallpox a nurse is a necessity if the patient is to be kept comfortable. In no disease does the comfort, the future eyesight, and even the life of the patient depend so completely upon the faithful ministrations of the nurse as in smallpox. The handling of the patient's body, covered with suppurating lesions, must be as gentle as possible and the strength of the patient must be conserved throughout. There should be an abundance of air space, a continual supply of fresh cool air, and a low temperature if this last feature is acceptable to the patient. In no acute disease, not even in lobar pneumonia, is it more essential to have abundance of fresh air.

In the *initial stage* of the disease treatment is often necessary to relieve the agonizing headache and general body pains. Sometimes these symptoms yield to mild measures such as the application of an ice-cap or a hot-water bag, but more often it is necessary to administer small doses of phenacetin, caffein or similar drugs or, what is more certain to relieve, moderate doses of Dover's powder or other opiate. Early in severe attacks it is wise to have the head shaved. This is particularly true in women patients. The procedure renders it comparatively easy to maintain cleanliness, while a better opportunity is afforded to make necessary applications. In nearly all severe infections the hair, in either sex, is lost during convalescence if it is unwisely preserved in the beginning. The likelihood of a good growth of hair returning later is much increased by proper attention to the scalp during the suppurative period.

The *mouth* and *throat* require almost constant attention during the eruptive stage in the confluent forms of the disease. Sometimes, especially

where there is much glandular swelling, the application of an ice-collar relieves, in part, the irritation of the pharynx and throat. Mouth washes and mild antiseptic gargles are a comfort, while drinks made of such substances as slippery elm, flaxseed or other soothing demulcent materials are relished when properly prepared and pleasantly flavored. Nothing, however, can take the place of careful, gentle and frequent cleansing of the teeth, mouth and throat. Small pieces of ice in the mouth at frequent intervals often prove soothing. Orthoform tablets, glycerine or other troches sometimes lessen the discomfort of swallowing and relieve the smarting pain. If there is intense pain on swallowing, which is frequent, it is helpful to spray the nose and throat with a 1 per cent. solution of cocaine with or without orthoform. A bland oil combined with aromatic substances is also useful as a spray. When the odor from the mouth is disagreeable, the addition of phenol or permanganate of potash to the gargles or spray is helpful.

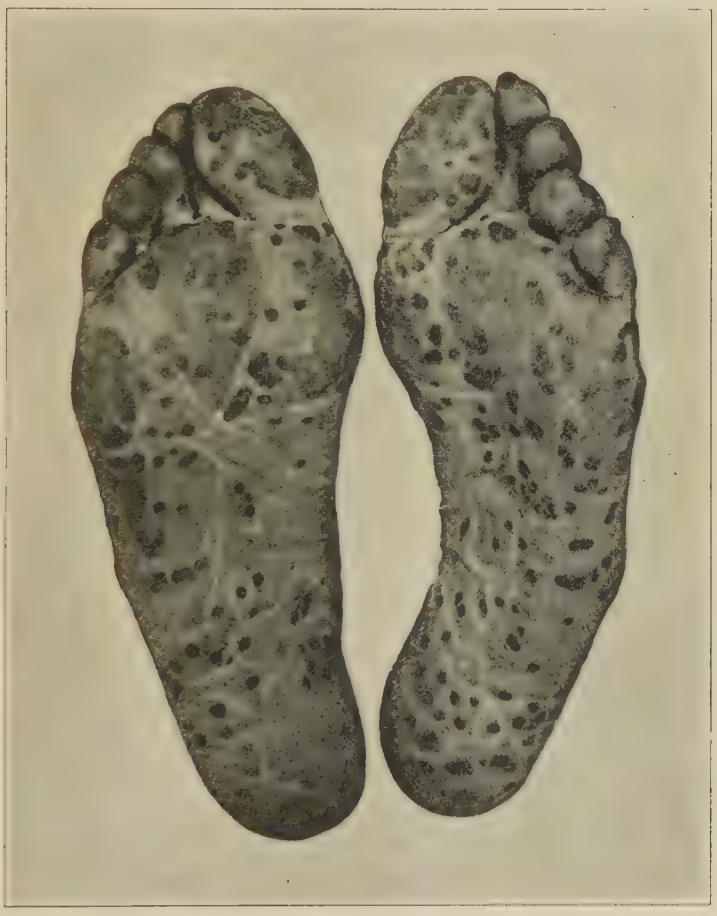
During the early days of the illness the patient does not, as a rule, care for food. Liquid diet at this time is advisable but as soon as the eruption has appeared a liberal amount of soft food should be allowed. Water and other drinks such as lemonade, orangeade, grape-juice, etc., should be given freely. For patients with delirium and great nervous excitement warm baths are very helpful and may be continued for hours and even for days with benefit. Sponging with cool water or alcohol and water is often refreshing during the febrile period. Two hot sponge baths daily are usually necessary throughout the attack. Insomnia is often a troublesome feature and is often due to the irritation of the skin; it is best controlled by hypnotics like chloral, luminal, veronal, etc., in small doses and if these fail by opium derivatives, preferably Dover's powder. An alkaline fever mixture does no possible harm and if the patient does not take fluids freely is helpful.

It is necessary, as a rule, that the eyes should be carefully and frequently bathed with weak antiseptic solutions. Saturated solution of boric acid or very dilute solutions of bichloride of mercury are most useful. Solutions of the silver salts are commonly used. Vaseline or other ointments when applied to the lid margins prevent them from adhering together and retaining pus. When there is a profuse discharge from the conjunctivæ the application of the solid stick of silver nitrate to the conjunctival margins is frequently helpful. Constant watchfulness for possible corneal ulceration is necessary, and if this occurs the pupil should be dilated with atropine. Hot applications are essential and the faithfulness with which these are applied is secondary in importance only to the early recognition of the condition. Many eyes are lost because of the general toxemia. In such cases the entire cornea sloughs and it is often necessary to enucleate the eye. Small ulcers of the cornea, discovered early, and given good care often yield to treatment. The application of an ointment of hydrarg. ox. flav. (gr. 2, 0.13 gm.), atropine (gr. 4, 0.25 gm.), vaseline (drams 2, 8 gm.) is often efficacious when applied to the eyelid twice daily. To quiet violent delirium it is often necessary and really imperative to give opiates. Large doses of morphine, hypodermically, frequently repeated, are often required. Chloral, the bromides and other

sedatives are of use, but are secondary in importance to the opium derivatives.

In severe attacks it is frequently necessary to force nourishment and to use alcohol to increase the food supply. There is, and probably always will be, difference of opinion as to the value of alcohol in smallpox. It is not to be used as a routine measure but is, in the writer's opinion, often

FIG. 14



Smallpox. Skin of the soles of the feet cast off in one piece and showing disks.

an invaluable aid in septic infection. In the true hemorrhagic form there is little hope of recovery, but the patient must be given every care and attention in the hope that the usual outcome will not result in that particular case. Considering how successful the treatment of certain obscure hemorrhagic conditions is by the intravenous use of human blood it is not too much to hope that eventually some similar treatment will

be successful in controlling even the hemorrhagic form of smallpox. For the average patient, after the initial headache and body pains are relieved, it is the local rather than the general treatment which is important. The eruption is usually distressing, although there are great variations in the discomfort. It is as important as it is difficult to avoid traumatic injury of the skin lesions. The itching is usually intense and at times is almost intolerable. This is particularly true toward the end of the suppurative stage. At this time both adult patients and particularly children must be watched, and if necessary restrained from doing injury to the skin lesions by scratching or rubbing. It is often necessary to both bandage and restrain the hands of children and adults during this stage.

The application of cloths thoroughly moistened with cold water to which glycerine is added and frequent changing seems to give the greatest amount of comfort. Tincture of iodine (10 per cent. in glycerine) painted upon the skin every other day until there is irritation appears to hasten the maturation of the pocks and certainly renders the patient more comfortable early in the attack. In some patients it is necessary to use much more dilute solutions of iodine, as the drug itself may cause a cellulitis. From the time the pustules mature the hot bath gives great comfort. Antiseptics and deodorants are often added to the bath with benefit. In the bath the crusts loosen and the pus is removed without pain. Linseed, starch or other poultices are often of use in softening the more persistent crusts, and prolonged hot baths containing carbonate of soda, frequently repeated, aid in the same purpose. The application of soothing ointments tends to relieve the irritation of the skin and softens the dry scabs. The hardened bits of epithelium in the palms and soles called "pits" and "seeds" are best removed, after thorough softening, by the point of some sharp instrument, such as a pocket knife. During the latter stages of the illness and convalescence boils and abscesses are very common. Such lesions should be freely incised when fully developed and the contents gently expressed. Hot applications to such areas frequently relieve the patient until such time as the lesion is sufficiently developed to require incision.

In closing the section on "Treatment" it is well to remind ourselves that the treatment of this disease, as is the case in diphtheria, scarlet fever and lues, is much less satisfactory than is the prevention. There is little excuse for the existence of smallpox and when a case does exist the fault must be divided between physicians, health authorities, legislatures and last and least the public.

CHAPTER II

VACCINATION

By GEORGE DOCK, M.D.

Definition.—Vaccination in the specific sense is the inoculation of the virus of vaccinia or cowpox for the prevention of smallpox. Efforts to substitute some other term, such as Jennerization, have failed to obtain wide use.

History.—Under the name of cowpox certain diseases characterized by vesicular or ulcerating lesions on the udders of cows have long been known in England and under corresponding names in other countries. The name was not limited to a single disease but applied to various diseases that have nothing in common but vesicular lesions. In some cases, however, the disease has the characteristics of inoculated variola or vaccinia; it spreads from cow to cow in dairies, and when it once enters a stable usually affects the majority of the animals unless they are immune from a previous attack. Edward Jenner[1] originally supposed that cowpox was derived from "grease," a disease of horses' heels, and that, transferred by dairymen who dressed the horses' heels and also milked cows, the virus became more fixed in the cows.

As regards cowpox, the probability is that this, in its specific form, is variola, derived directly or indirectly from human sources. The term "spontaneous" applied to some cases of cowpox is a bad one, since there is no reason to think that cowpox arises spontaneously any more than smallpox. As a rule the source cannot be found, but remembering the tenacity and wide spread of smallpox, the relation can hardly be doubted. Numerous experiments show that, while failures occur, it is comparatively easy to infect many species of animals with variola or vaccinia.

It was known to dairy-workers long before the time of Jenner that cowpox protected against natural or inoculated smallpox. In various parts of the world, at different times, a number of persons made experiments with the inoculation of vaccinia to protect against smallpox. None of these detract in the least from Jenner's claim to immortality, for none of them led to a wide or general use of vaccination. Although his observations and experiments were few in number, they were more numerous than those of his forerunners, and were carried out with a scientific accuracy far ahead of the contemporary knowledge of infectious diseases. Formerly a rare operation, Jenner made it of world-wide use, and showed the possibility of carrying the virus through the human body and becoming independent of natural cowpox, an essential step in the development of vaccination.

[1] "The works of Edward Jenner and their Value in the Modern Study of Smallpox," by George Dock, *New York Med. Jour.*, November 29 and December 6, 1902.

Jenner's first work, *An Inquiry into the Causes and Effects of the Variolæ Vaccinæ*, appeared in the summer of 1798 and additional observations and conclusions early in 1799. By 1800 the operation was carried out in most parts of Europe and in America, where Waterhouse, of Cambridge, had taken it up with enthusiasm; and it was used very early in the world-wide Spanish colonies.

Very early Jenner established the following points: The protection of vaccination against smallpox, whether acquired in the natural way or by inoculation; the importance of using virus only from typical and regularly progressing vesicles free from suppuration or other complications; the advantages of a clean and simple operation; the possibility of partial or complete failure, with the indication for repeating it (or in case of need even variolating); the importance of special knowledge, experience, and careful observation in all cases. He realized that severe local lesions do not indicate protection, but may even be harmful. Jenner's great error was his belief in the life-long immunity conferred by vaccination; and yet if it had not been for this fallacy he probably would never have given vaccination to the world. The consequences of the error have not yet been overcome by the medical profession; but for this Jenner should not be held responsible.

Coincident with the rapid spread of vaccination was a marked fall in the extent and mortality of smallpox all over the civilized world. As an example, in London in the years 1761–1800 the mortality in the successive decades was respectively 24,234, 20,923, 17,867, 18,477. In the first two decades of the nineteenth century it was 12,534 and 7856. Toward the end of the second decade of the nineteenth century smallpox began to increase, and in some countries became almost as prevalent as before. The causes of the recrudescence are not difficult to understand. Many people had been vaccinated so long before that they had lost their immunity wholly or in part. This was the time to settle the question as to the life-long protection which the early vaccinators so fondly believed in, but prejudices were still too strong. Many other people were not vaccinated at all, because smallpox was so much less frequent that the operation seemed unnecessary, and there was a smaller proportion than before not protected by smallpox. Smallpox existed in many places as no efficient effort had been made to stamp it out, and it was even kept up by sporadic variolation, not prohibited in England until 1840, five years later than in Prussia. Whenever the disease prevailed some vaccinated people were sure to take it, and many were the efforts to reconcile this with the sweeping claims of the early vaccinators. Imperfect vaccination, degeneration of lymph, new types of disease, the cowpox not the genuine kind, or the smallpox not real smallpox—such were the explanations; but the practical lessons were learned very slowly. Looking back it is clear that certain great changes had occurred in the smallpox situation since Jenner's discovery. The absolute mortality was less; the disease was not so frequent as before in the years following the usual age of vaccination; and these facts were most obvious in countries that had the most thorough vaccination. The change in the age-incidence is interesting. Smallpox was commonly spoken of in Germany in the pre-

vaccination days as "Kinderpocken." Of 1252 cases of smallpox before vaccination 94 per cent. were in children less than ten years of age, and no case above twenty. Of 1677 cases after vaccination only 18 per cent. were under ten years of age, and 42 per cent. over twenty. Epidemics were smaller, and mild cases, long known but rarely mentioned, became relatively more frequent. The recognition of varioloid as a mild but genuine form of smallpox was a great advance over the time not long before when each variety of smallpox was looked upon as a distinct disease, not protected against by vaccination.

In this period *revaccination* began. Suggested early in the century, it was long neglected. Certain German states first applied it to their armies. Würtemberg, after a trial in 1829, made it obligatory for recruits in 1833; Prussia in 1834. Some other German states did not adopt it until the 60's. The most striking test of the possibilities of vaccination was made in the war of 1870–71. Smallpox became so prevalent in France in the preceding winter that efforts were begun to combat it, but the outbreak of the war not only prevented such action, but as usual caused a great increase of the disease, which rapidly extended over Europe. In Germany, where many prisoners of war carried the infection, the disease was widespread; but it was a striking fact that the German soldiers were not only less frequently and less severly affected than the French, but that they were less affected than civilians of military age in the same towns. The only difference was that all the German soldiers under arms at the outbreak of the war had been revaccinated within two years. The following figures show the mortality of different classes at that time: revaccinated 5 per cent., once vaccinated 14 per cent., unvaccinated 45 per cent. This object lesson was not lost on the German Empire. In 1874 the first law was passed providing for the vaccination of every child before the end of the second year, and of all school children in the twelfth year. The result of the operation was to be a matter of record, and failure to produce a satisfactory vesicle necessitated a repetition. In the civil population the mortality sank rapidly, so that in 1910 the deaths in the whole empire were only 33 (15 being foreigners).

In the meantime other important events had taken place. The continued existence of smallpox was ascribed to degeneration of lymph, and this was sometimes obvious in the poor development of the vesicles. This led to efforts to obtain stronger virus. Cowpox had become very rare, and though rewards were offered in some countries, few cases could be found. Retrovaccination, or the inoculation of the cow with human virus, was used to revive the stock, but not with the desired success. Numerous experiments demonstrated that vaccinia is variola in the cow. Inoculation of calves with smallpox material, with proper care, produces a disease indistinguishable from primary or "spontaneous" vaccinia, and giving the same protection against both smallpox and vaccination that natural cowpox gives. The contradictory results of the Lyons commission, which believed that variola inoculated into animals remained variola, with all its dangers, are now believed to have been based on technical errors. Inoculation of the first remove of such material is likely to produce severe effects, such as intense local reaction, general

eruption with secondary fever, or even death (Chauveau). But after several transfers through cows the infectious character is lost, secondary fever does not follow inoculation, and the material can be made to retain its characters without bad results.

Etiology.—Since vaccinia is then believed to be smallpox, altered by its passage through the cow, the etiological factor must be the same, modified in virulence if not in morphological characteristics. In fact the history of the search for the cause of vaccinia is part of that of smallpox. Like the latter, vaccinia has been investigated by all known methods and there is reason to believe that the search has reached a point very near success. The bodies found by Guarnieri in 1892 have been studied by many others. All describe certain alterations in epithelial cells in vaccinia as well as in variola. Early investigators supposed these to be pathogenic parasites, but they are now believed to be products of cell degeneration, specific morphologically. Gins, however, thinks they are independent foreign organisms occurring not only in the epithelial cells but also, in the rabbit's cornea, between them. The general belief is that the Guarnieri bodies are caused by more minute bodies termed "elementary bodies" by von Prowazek, often called "Paschen's bodies." These are 0.2 to 0.4μ in diameter, occur in the cells and in the plasma, both in variola and in vaccine lesions, and in the latter can be found about two hours after infection. Von Prowazek assigned them to the chlamydozoa, Hallenberger to the monera, organisms between bacteria and protozoa. Lipschuetz has proposed the name strongyloplasmata for this class of organisms. The term invisible often given to such bodies may depend upon difficulties of staining, peculiarities of refraction, possibly degenerations in drying or in staining. They are able to pass through porcelain filters but are stopped by colloid. Levaditi thinks the behavior in filters does not depend upon a disproportion of germs and pores but on adsorption. Van Heelsbergen (1922) has published some observations going to show that the virus of smallpox, vaccinia, spontaneous cowpox, stomatitis of horses, fowl pox, and fowl diphtheria are all varieties of an original virus, some of them so undifferentiated that they can pass from one form to another. Noguchi and others have shown that the vaccinia virus can develop in the testes of rabbits. Levaditi and his co-workers and many others have propagated it not only in testes but in the brains of animals ("neurovaccine") and in both cases characteristic vaccine virus has been obtained. The central nervous system in such experiments acquires a tissue immunity to vaccinia and also allergic qualities like those in the skin. After many passages through the brain the virus acquires such an affinity for nervous tissue that 0.2 c.m. of a 1 to 10 million dilution injected intracranially produces a fatal encephalitis. Levaditi thinks the ectodermal origin of the nervous tissue explains the high pathogenicity of vaccine virus in it as compared with other ultravisible germs.

Plotz (1922) reports the cultivation of vaccine virus in Smith-Noguchi medium anaërobically, in several generations, immunizing rabbits with the cultures and obtaining a positive complement fixation with vaccine antigen.

Although *bacteria* are no longer believed to be the specific agents of vaccine, they are of great importance in the pathology and still more in the practical application of vaccinia. Lymph from young intact vaccine vesicles is sterile, but in lymph as ordinarily examined, bacteria of various kinds may be found, both in the calf and in the human vesicle. Most of them are harmless saprophytes, but pathogenic forms are not rare, though usually not very virulent, as the great majority of vaccine operations prove. Streptococci are rare, but have been found in the benign vaccine pustules in children.

Histology.—The investigations of Pohl-Pincus (1882), Unna (1882), and others, and more especially the studies by Howard and Perkins,[1] give us a fairly clear idea of the histology of the vaccine lesion. It begins as a hyperemia which increases in the purulent stage. Degeneration of epithelial cells, with swelling and vesiculation or reticulation, occurs, especially in the middle part of the prickle-cell layer. The remains of the puncture, if one has been made, show as a cleft filled with blood corpuscles, broken-down cells, and fibrin. Necrosis of cells forms columns that run down through the centre of the lesion, and the dropsical degeneration begins near these. The prickle cells become smooth. At the end of twenty-four hours the epithelium shows swelling, but not macroscopically. Howard and Perkins found vesiculation far advanced at forty-eight hours. The reticulum, made up of fine and coarse fibers, can be traced to hyaline fibrinoid degenerated epithelial cells.

As the process advances, hydropic degeneration affects all the layers of the epithelium, and may extend to the corium. Nuclear changes then become more prominent, with numerous mitoses, often atypical, and with various forms of degeneration of the chromatin. At the margins of the vesicle the cells are often swollen and their prickles lost. Cell inclusions may be seen. Red blood corpuscles and leukocytes occur in the degenerated tissue at the base and sides of the vesicles, eosinophile cells being often numerous. Changes in the corium are more marked than in variola. Œdema, leukocyte infiltration, and vascular changes, are described by Howard and Perkins. The sweat ducts and hair follicles are often unaffected by the dropsical degeneration, though polynuclear cells appear in them, and the ducts, with the degenerated cells along the seat of inoculation, show as strands among the hydropic cells and account for the umbilication. By the fourth or fifth day in the calf (Steinhaus), the fourth in man (Howard and Perkins), the vesicle ceases to increase in diameter, but becomes elevated from liquefaction of its contents. In the liquid contents are broken-down cells, free nuclei, and débris. As the epithelial cells liquefy, a gradually increasing immigration of leukocytes takes place, from about the third day, causing the contents to become turbid and purulent, and obscuring the histological features of the lesion. On the sixth day the pustular change is complete; the cellular strands begin to break down. On the fifth, sixth, or seventh day desiccation begins. The epidermis grows in from the sides, with numerous nuclear figures, gradually raising up the scab.

[1] *Jour. of Med. Res.*, 1905, **14**, No. 1.

Howard and Perkins could find no bacteria in the lesions they examined from the second to the seventh day, and they conclude that mixed infection with bacteria plays no part in the production of the lesions of human vaccinia when the operation is carried out under proper precautions. These observers conclude that the degeneration and exudation "are due to the action of a powerful soluble toxin which acts very much like diphtheria toxin. It would appear that immunity production is intimately associated with the setting free of this poison in the lesion, for the œdema and other inflammatory changes persist long after the process in the epidermis has ceased to extend."

Vaccine Virus.—The older methods of obtaining vaccine virus are described in earlier editions of this work. At present the virus is propagated in animals, calves or heifers being used, females being preferred, and light-haired ones on account of their clearer skin. The age is usually three to six months, though it varies from one month to two years. The animals must be sound and well, and, in order to avoid inoculation during accidental disease from travel or change of conditions, should be under observation for a few days. Tuberculin and other tests are unnecessary, as it is customary to kill the animals before the vaccine is used, and the autopsy furnishes more accurate information. Vaccination does not lessen the value of the animals for food.

The calves are cleaned as thoroughly as possible before they are taken to the operating room. They are then fastened to a suitable table and the abdomen is shaved and washed with soap and warm water. Antiseptics have been used but are not necessary. The final washing is done with large quantities of sterilized water and the skin dried with sterilized towels. The operators, in sterilized clothing, observe the usual rules of asepsis. A series of incisions is made in the prepared skin, one-half to one inch apart. The area treated varies in different institutions, sometimes extending from the inguinal folds to the level of the navel, sometimes to the axillary folds. Other areas, such as the escutcheon or the scrotum, are sometimes inoculated. The sides and back are generally not used on account of the toughness of the skin. If more than slight bleeding occurs it is checked by pressure with sterilized towels. The "seed" vaccine is spread over the prepared surface and allowed to dry. The seed is of various kinds, either glycerinated bovine virus selected with care from particularly well-developed vesicles and of tested bacterial purity, selected humanized virus, or material derived more or less remotely from human variola. Some of the best strains in Europe are of this kind. It would be of great scientific interest and some practical value to have records of all vaccine strains, but makers often do not know or are unwilling to state the sources and nature of the seed.

The material is gathered between the third and sixth days, most frequently in one hundred and twenty hours, when the vesicles are well-developed but show no evidences of suppuration. The animal is put on the table, the abdomen thoroughly washed with warm water and soap, rubbed by hand, finally washed with sterilized water, and dried. This removes the dried superficial epidermal scales and does not break the

vesicles. For the removal of the pulp a large curette is drawn along each row of vesicles, taking these off very thoroughly without much contamination with blood. After the pulp is all secured, it is ground in a special mill under aseptic precautions, in order to render it homogeneous. It is then thoroughly mixed with glycerin and kept for several weeks to "ripen" at a temperature of 10° F. The object of the glycerin is to destroy the bacteria, either in the vesicles at the time or accidentally introduced into the pulp. Glycerin was early recommended as a diluent for vaccine virus, and to reduce its viscosity and prolong its activity.

Copeman proved that in glycerinated pulp the bacteria become gradually reduced in number, and even disappear at a time when the specific agent is still unimpaired. Drying has a similar effect on vaccine, but glycerin has the advantage that besides dehydrating the germs, it permits the formation of a homogeneous emulsion, part of which can easily be tested, and so permit accurate conclusions as to the qualities of a large amount of lymph. The mode of action of glycerin has long been a problem. Janzen and Wolff (1923) have shown that it may be associated with d' Herelle's phenomenon. In glycerinated virus the specific action has been found present after one year, but it may become inert within a month after the bacteria are killed, especially if the virus is exposed to ordinary summer heat. Great dilution does not destroy the practical efficiency of glycerinated lymph. The usual proportion is about 1 part of lymph by weight to 10 parts of 50 to 60 per cent. chemically pure glycerin with 0.1 per cent. clove oil. The acidity of the mixture is corrected with sodium carbonate. Dilutions of 1 to 2000 have given good results. One calf may furnish 3000 to 5000 portions, and perfect vaccination has been obtained from lymph representing one fifteen-thousandth of the yield. But this gives only the favorable aspect of the glycerin. Its effects on the bacteria and on the specific germs are modified by other factors. Glycerin acts best on bacteria at a temperature of 37° C. or above, very little at low temperatures; but the vaccine germs are injured by temperatures very little above 37° C., though they resist cold to a remarkable degree. Moreover, the bactericidal action of the glycerin is imperfect in practice, so that careful tests are necessary, even if the ripening has been carried out for the usual time of four to six weeks.

Valuable as glycerin has been, it does not obviate the need of scrupulous cleanliness, and until we are able to cultivate the specific organisms pure, efforts should be made to find a better agent. Chloroform (Green, 1903), potassium cyanide, more recently eucupinotoxin-glycerin (1 to 5000) all give promise; further results, with the last especially, should be followed.

Glycerinated lymph is generally dispensed in small glass tubes, each containing enough for a single operation, with a sterilized needle and a rubber bulb for expelling the lymph. Since 1910, the sale of dry points has been prohibited in the United States. Under the Act of Congress of 1902, regulating the propagation and sale of virus, an improvement in purity and potency of vaccine preparations has come about.

The preparations are rarely free from bacteria. The examinations

of Rosenau and many others rarely show no growth, but the number may be very small. It seems quite possible to reduce it to less than 20 per preparation. In "poor" vaccine there may be from several thousand to a number too large to count. Vaccine in all forms, dry or glycerinated, is capable of deterioration from a number of causes. Kept free from bacterial contamination and at a low temperature, the virus remains active for many months. High temperature is likely to weaken or even destroy the activity of the virus. Accordingly, lymph should always be kept in a cool place, including the time of transportation, and should not be used at all if more than three months old.

The question of the relative strength of bovine and humanized virus is not a simple one, because there is no constant standard for either, and the proportion of takes with the two kinds varies greatly. Much humanized virus was almost or quite inert in the days when it was the only kind used. Bovine virus also may become weak. Weak virus seems attractive to some, but its use goes far to defeat the object of the operation and to give opponents of vaccination arguments against its value. The ideal should be the most intense specific action compatible with a safe local lesion.

The practical advantages of bovine virus are obvious. It permits selection and cultivation of seed more than does human vaccine. It can be prepared in large quantities, at short notice. It is free from the danger of syphilis, and with proper safeguards can be made as harmless, bacteriologically, as human virus can. The chief disadvantage is the possibility of contamination with pathogenic germs; but this can be wholly avoided by careful examination of material before it is used.

The Operation.—The first method, and that of Jenner himself, was simply an imitation of the variolous inoculation. Punctures or short incisions were made and the virus inserted. Later, blisters were raised on the skin and the virus placed on the abraded surface. The incisions were increased in number, then cross-scratches were made, and finally the operation became a denudation of the epidermis, sometimes of very considerable extent. The disadvantages and dangers of such a method are obvious, for while it is possible to abrade so superficially that the vaccine will take and yet the epidermis heal over before the vesicle forms, as usually made the abrasion is followed at once by a scab of more or less thickness, under and around which the lesion must develop. The scab not only interferes with the development of the normal vesicle, but is irritating and induces rubbing or scratching, which promote secondary infection and give the most favorable conditions for the development of infections from germs previously in the skin or introduced in or with the vaccine. Tetanus especially may be expected to flourish under just such conditions.

The *point of election* for vaccination is the outer surface of the upper arm, over the insertion of the deltoid muscle. This is not only convenient for the operator but also for the patient during the development of the lesion, and it seems less likely to be followed by severe glandular complications than are many other parts. The leg is sometimes vaccinated in order to avoid the disfiguring effect of a vaccine scar. In regard to

this it should be said that a normal vaccine scar is not a deformity, and on the other hand any part of the leg is more exposed to trauma, and therefore to complications, than the upper arm. The writer always refuses to vaccinate on the leg unless the patient will stay in bed until the vesicle has healed, an objection that never fails to change the situation. If the leg must be vaccinated, the operation should not be done on the front of the thigh, but on the calf below the head of the fibula. Jeannerrets' suggestion, to vaccinate on the feet in young infants, has something in its favor.

The *number* of insertions has an important bearing on the probability of taking, as well as on the protection. The German regulation of 1899 requires at least four incisions, each 1 cm. long and 2 cm. apart. The Local Government Board of England directs that four vesicles should be produced and that the total area of vesicle formation should be not less than half a square inch. With lymph of known potency a single insertion will do for a primary vaccination and for most revaccinations. In case of exposure to smallpox or with a history of failure in previous operations, when there is doubt as to the potency or when there is danger that the subject may not return for observation, two, three, or four insertions should be made.

"Vaccination is to be looked on as a surgical operation and carried out with all the precautions necessary for the prevention of septic infectious disease. Especially must the physician carefully consider the cleanliness of his hands, the instruments, and the place of operation" (German requirements of 1899) The seat of the operation must be clean and not treated with the usual antiseptics; acetone may be used without danger of affecting the virus. Usually it is enough to clean the skin with sterilized water, but if the arm and the clothing are dirty the arm must be thoroughly washed with soap and water.

The *methods of operation* are all based on the use of liquid virus. The usual ones are incision, abrasion, puncture, and intradermal injection. Many experiments have been made with the introduction of vaccine virus subcutaneously, intravenously, by the peritoneum and the alimentary canal. Immunity can be produced by all these methods, but requires larger doses, is slower and less frequently successful than the cutaneous route.

In the *incision method* a scalpel is used, sterilized by dry heat, steam, or boiling. The incisions should not be deep enough to draw blood in large drops. Minute drops do not interfere with the take. A little practice enables the operator to estimate the toughness of the skin and the sharpness of the blade. Only one incision is made for each vesicle desired. The incisions should not be more than 1 cm. long and not nearer than 2 cm. apart. With potent virus $\frac{1}{2}$ cm. is long enough. The capillary tube containing the lymph is removed from the package, one end inserted through the small rubber bulb, the end beyond the bulb broken off and that end withdrawn into the bulb. The other end is then broken off. In breaking the tube it should be covered with a piece of sterile gauze to prevent small splinters from flying off with danger of accidental infection. With the tip of one finger over the puncture in the bulb the latter is com-

pressed and the virus expelled over the incision or incisions. It is then gently rubbed, not ground, into the incisions, using the side of the capillary tube, and allowed to dry without exposure to sunlight or high temperature. Dressings are not necessary in the beginning. Pads, plasters, and shields increase irritation by heat and moisture, often cause softening and breaking down of the epidermis, provoke infection of the neighboring skin or even of distant parts, by rubbing, and may lead to other traumatisms. If the clothing is not perfectly clean a piece of sterilized muslin should be pinned on the inside of the sleeve to protect the site of operation. Bathing need not be omitted or any ordinary occupation avoided. A clean incision quickly heals. The normal vesicle has a tough skin and cannot easily be broken before it is mature. If a vesicle becomes broken, a light protective dressing, not more than four thicknesses of aseptic gauze, should be put over the wound in such a way as not to rub. Collodion or narrow strips of adhesive plaster can be used, but only along the edges of the gauze. If a vesicle becomes infected it should be treated like any other infected wound and by no means neglected for fear of ruining the vaccination. It is better to repeat the vaccination than to allow an infected wound to go untreated.

In the *abrasion method* a Pirquet drill is used, not more than 2 mm. wide, either on the dry clean skin or through the drop of lymph, placed on the skin as described above. A single turn of the drill, bringing out a bluish color in the epidermis, suffices and the wound quickly heals. Inexperienced operators make the abrasion too deep and produce a hard irritating scab.

For the *puncture method* any plain sewing needle can be used. The sterilized needle furnished with the tube of vaccine is most convenient. In vaccinating on a large scale the virus may be obtained in bulk and a number of needles may be used, sterilizing by boiling after each operation. The lymph should be blown on to the skin as described above in one or more drops, as desired. Five or 6 punctures are then made through each drop within an area of about 2 mm. in diameter in each case. With the skin put on the stretch with the thumb and finger, the needle is inserted perpendicularly or obliquely just into the true skin. In subjects with rich skin capillaries blood may appear. The lymph should be allowed to dry as in the other methods without exposure to sun or heat.

After many experiments in subcutaneous vaccination the *intracutaneous method* was tried and has been practised by a large number of competent operators. Leiner and Kundratitz[1] showed that by it a typical reaction could be obtained, "differing from that of cutaneous vaccination and easier to observe than that following subcutaneous vaccination" (J. H. Gettinger[2]). In the usual practice 0.1 c.cm. of glycerinated lymph is used, diluted with 3 to 10 times the bulk of physiological salt solution or sterile water. Many prefer to draw the virus into the syringe with one needle, remove that, expel the air, and then attach a fresh sterile needle to prevent epidermal inoculation. E. S. Safarik of the Los Angeles

[1] Die intrakutane Impfmethode mit Kuhpockenlymphe beim Menschen. *Ztschr. f. Kindhlk*, 1921.

[2] *New York Med. Jour. and Rec.*, 1924, **120**, 115.

General Hospital has demonstrated the possibility of avoiding such infection by flaming the needle after filling the syringe. The skin is disinfected with iodine. The needle, 25 to 27 gauge, is inserted into the cutis about 1.5 cm. and the lymph injected, producing a wheal which soon disappears. The needle should be deep enough not to show through the skin. When it is withdrawn the puncture is again touched with tincture of iodine and washed off with alcohol.

The *reaction* begins in twenty-four hours as an erythematous nodule 6 to 10 mm. in diameter, deep red in the centre and paler at the periphery. Sometimes the area is pear-shaped with the narrow end at the puncture. The redness and swelling last a few days. A second reaction begins about the tenth day, develops rapidly, usually reaches its height in three days, and lasts for ten to fourteen days. The swelling is from 20 to 30 mm. in diameter, is chiefly in the subcutis, movable at the base but attached to the skin above. By the third week the infiltration subsides, the color fades, being displaced by discoloration which disappears in six or seven weeks. There is little or no rise in temperature. The soft induration contains sterile pus, the axillary glands are tender and swollen. The reaction usually shows two phases, the first in twenty-four to forty-eight hours, the second from the tenth to the fourteenth day and after the complete disappearance of the first reaction. It is in the second phase that immunity is developed. As Gettinger says, intradermal vaccination produces less constitutional reaction than cutaneous vaccination; it eliminates the possibility or at least greatly lessens the risk of secondary infection; it removes the danger of accidental vaccination in other parts of the body. It can be used in the new-born and in early infancy, in patients with skin diseases, in the insane and in those who would be likely to destroy a cutaneous inoculation, and can be done at any season of the year. It has the great drawback of not leaving any record in the form of a scar, which scar in the writer's opinion is not necessarily disfiguring.

Clinical Features of Vaccine in Man.—The best indices of the efficacy of vaccination are the course of the vesicle, the general symptoms, and the scar. Ultimately we may learn more exact guides to the immunizing power of vaccine, but at present we can only say that if the vesicle and scar are characteristic there is more or less immunity; if they are not characteristic, we must admit that immunity can not be considered present. The importance of knowing the characteristics of the vaccine lesions is therefore obvious. It is chiefly on account of the great diagnostic value of the vesicle and scar that subcutaneous methods of vaccination are not to be commended.

Typical features of primary vaccinia are much alike in successful cases. For this the subject must not have been previously vaccinated nor had smallpox. The virus must be potent and the best test of this is the clinical application in other primary cases, which is more trustworthy than inoculation in the cornea or skin of animals. This information should be obtained from health officers or others who vaccinate on a large scale. It should never be forgotten that total failure of reaction suggests that the virus is not potent rather than that the subject is immune.

The stage of *incubation* lasts about three days. The site of inoculation may heal at once or may show a simple traumatic reaction. By the end of the third day a papule appears, 1 to 2 mms. in diameter. It is rounded but soon becomes flattened with increase in size, round or oval in outline, depending on the shape of the inoculated area, of a bright red color, feels hard, and is superficial. By the fourth or fifth day the top becomes vesicular and a central depression ("umbilication") rapidly develops. By this time the skin around the vesicle is deep red and slightly swollen and this "areola" or halo grows wider as the lesion becomes mature. By the end of the seventh day the vesicle has reached full size. It is round or oval, flattened on top, and umbilicated. The top is whitish, yellowish, grayish, or bluish, sometimes compared with pearl or alabaster. The sides are sloping, the skin around the base a deep red, 1 to 2 cm. wide, and beyond this sometimes a red but paler zone which passes gradually or abruptly into the healthy skin. The contents of the vesicle are clear and watery and somewhat sticky. If punctured the multilocular character can be demonstrated. By the eighth day the vesicle becomes yellowish, the middle part is sometimes fuller for a short time but in a day or so sinks down from desiccation (secondary umbilication). The areola is often redder at this time, 2 to 3 cm. or more in radius, the surface rough like orange peel, the edge often sharply circumscribed. It is indurated, sometimes rather deeply. The outline may be very irregular with islands of red skin adjacent. The appearance is strongly suggestive of erysipelas. In severe cases the arm is swollen, the skin feels hot, the axillary glands are large and tender. From the ninth day the areola fades, sometimes becoming yellowish from altered blood. The swelling subsides. The period from the eighth to the eleventh day is most significant and in that time the subject should always be seen. From the eleventh or twelfth day the vesicle dries rapidly, forming the "scab," which is brown, hard, and wrinkled or fissured. Finally, sometimes not until the end of the third or fourth week, the scab becomes loose at the periphery and falls off. The resulting scar at first is deep, the edges sharply defined, the floor flat and deep red. It slowly grows pale, approaches the level of the skin, and shows distinct pits or "foveations," one of the essential features of a successful vaccination. The final size of the scar is much less than that of the recent state or the mature vesicle.

The *local sensations* associated with the development of the vesicle vary much in different individuals. Some do not complain and show no evidence of rubbing or scratching. Others, who do not seem more severely affected, complain bitterly, and can not be prevented from rubbing, scratching, or tearing at the skin. During the height of the development of the vesicle the patient often, but not always, experiences more or less malaise, loss of appetite, sometimes nausea or even vomiting, headache, and pain in muscles and bones or in the lumbar region.

As regards the body temperature Hennig and Bohn found a slight rise—0.5° to 0.7° F. in the first three days—but Sobotka could not. If present it is doubtless due to irritation of the wound. From the third to the seventh day the temperature is remittent, rising a few degrees, and remains about this point but with less marked remissions for two

or three days longer, and then rapidly falls to normal. The fever does not seem to bear any proportion to the size and number of the lesions, provided they are not complicated, but is closely related to the areola, according to Bohn. Pirquet points out that the temperature is more variable than the other clinical features. Severe nervous symptoms, especially convulsions, do not occur. Huguenin looks upon fever as an essential part of vaccinia, as Zaehrer (1846) did long before. According to him children who do not have fever must be vaccinated again, but Sobotka in a few cases could find no definite elevation of temperature in the vaccinated new-born. Vaccination after a take does not alter the characteristic curve, nor does opening the vesicle (Sobotka). The nitrogen excretion is increased for a short time about the tenth day, and diminished later.

The red blood corpuscles and hemoglobin show no distinct anomalies but the leukocytes are increased. In primary vaccination Sobotka and Enriquez and Siccard found a leukocytosis of as much as 23,000 the former with the polynuclears, the latter with the mononuclear cells increased; myelocytes were rarely present. Billings found a maximum count of 15,000 leukocytes, with the neutrophiles especially concerned, most from the sixth to the eighth day, and disappearing in two to four days more. Sobotka also found an early leukopenia, and a secondary leukocytosis, beginning about the tenth day, with an intermediate low leukocyte count. Courmont and Montagnard saw nothing abnormal in the blood in adults, and Enriquez and Siccard found the blood negative in generalized vaccinia. Sobotka calls attention to the resemblance of the blood changes to those in variola.

Revaccination. – Experiments and observations on revaccination in the past few years have thrown much light on the results and some that were dismissed as insignificant variations are now given cardinal importance. In the writer's opinion the classification of J. N. Force is most useful. It includes three types of reaction: The primary already described; the secondary or accelerated, formerly called vaccinoid; and the immune reaction. Although in some cases it may be difficult to draw a line, a broad study of the varieties will enable the operator to properly record results in each case.

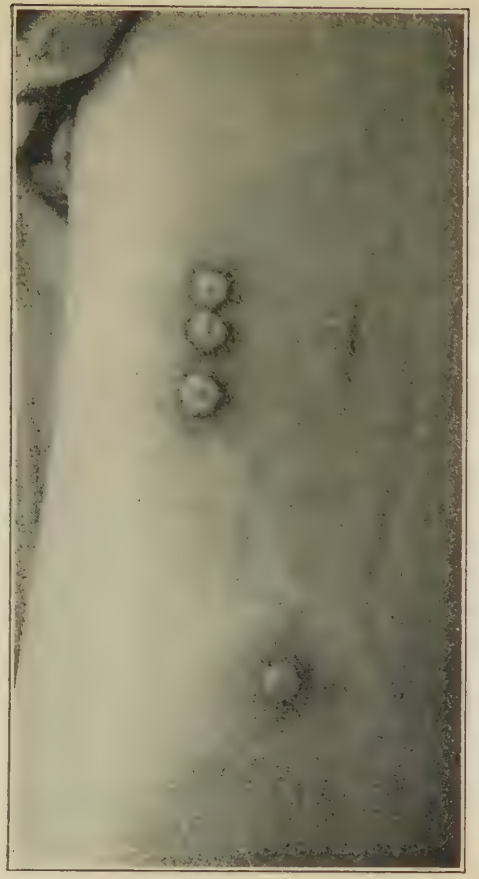
Accelerated Reaction. — If there is no immunity the results are strikingly similar to those in primary vaccination but the various stages are more or less shortened, the incubation lasting about three days and followed with rapid development of papule, vesicle and areola, with mature vesicle at the end of the seventh day. There is usually fever on the fourth day, pain and swelling of the axillary glands on the sixth, induration of the areola on the seventh and eighth, sometimes with swelling of the upper arm. The fever ends at the tenth or eleventh day and may reach as high as 104° F. The phenomena are most marked when revaccination is done after a long interval. With more or less immunity remaining the process may be shortened and all the phenomena less marked than in primary vaccination. For such cases the term accelerated reaction seems better than "vaccinoid," but in every case the date of the height of the reaction should be observed and recorded.

Immune Reaction. This was long overlooked because vaccinated subjects were usually seen, if at all, a week or more after the operation. If observed it was usually confused with the various imperfect results indicating little or no immunity. On account of its importance all revaccinated subjects should be seen at the end of twenty-four hours after the operation and again in forty-eight hours. The reaction begins from ten to twenty-four hours after operation as a definite area of redness, swelling, and induration. The features can be observed better by making a control operation with sterile salt solution before the real operation. There is itching, sometimes very troublesome, but very little soreness. The height of the reaction may not occur until thirty-six to forty-eight hours, after which all signs fade, and in a week or more the skin shows little or no alteration.

It is most important to have accurate observations and records of the results of all vaccinations. Unfortunately operations on the general public usually fail in these respects, but in school children, soldiers and sailors, inmates of asylums, and all others vaccinated on a large scale, a formal record should be kept. This should give: The name of the subject, address or means of identification, date of vaccination, make and number of the virus, number and condition of existing scars, type of operation, date of inspection, and the result, noting primary, accelerated, immune, or failure. In careful investigations the time of the greatest extent of redness and swelling should be noted. It is a great assistance in such cases to make an accurately measured outline and a corresponding profile of the various parts of the reaction. The important periods for observation, as Leake points out, are in immune cases the first to third day, with accelerated reactions the fourth to eighth day, and in primary vaccination the ninth to eleventh day.

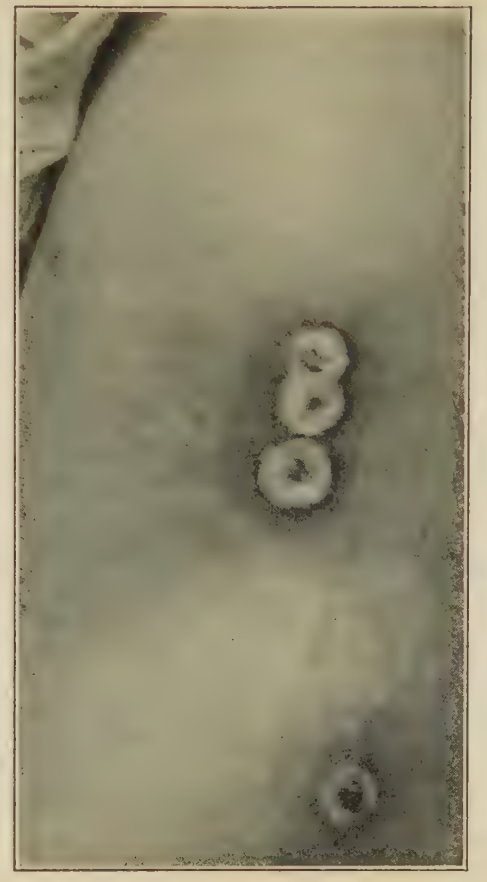
Experimental Features of Immunity in Vaccination.—Important conclusions may be drawn from the many experiments carried out on the cornea and skin of rabbits and other animals, and by other methods. Some of the most important data are as follows. By cutaneous inoculation rabbits acquire skin immunity to vaccinia that lasts several months. So also corneal inoculation makes the cornea strongly immune. Subcutaneous inoculation produces cutaneous immunity but only imperfect immunity of the cornea. Inoculation of the skin gives immunity to the cornea but it appears later and is weaker than the general immunity on which it probably depends. Corneal inoculation gives cutaneous immunity but it is weaker and slower to develop than the immunity of cornea and skin after cutaneous inoculation. Inoculation of both corneas confers stronger immunity than that of a single one and inoculation of one cornea gives only feeble immunity to the other. After cutaneous inoculation virulicide antibodies appear in the blood in varying amounts. Sometimes serum diluted 100 to 200 times completely inhibits potent lymph, but after a few months the antibodies become weak or disappear. After corneal inoculation antibody formation is less constant and weak. In rabbits revaccinated after the disappearance of the antibodies, the latter are renewed although traces of immunity prevent a visible reaction. Two young rabbits from a mother immunized by

Fig. 15



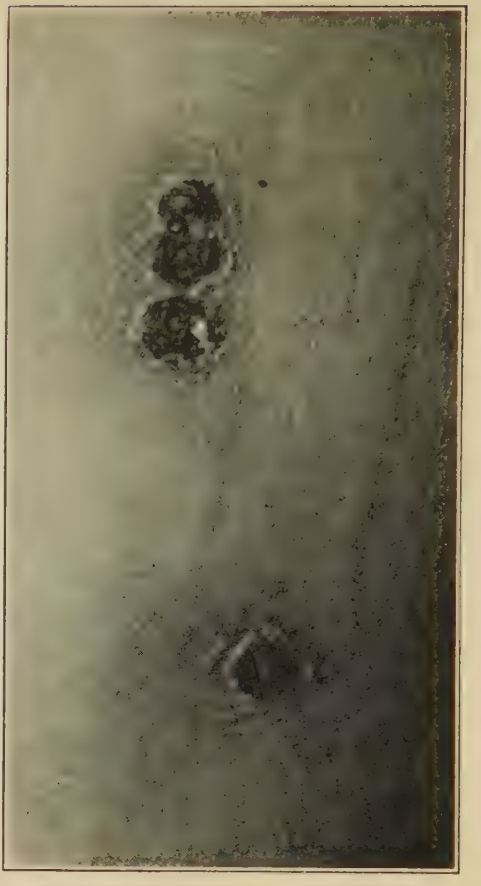
Fifth day.

Fig. 16



Seventh day.

Fig. 17



Twelfth day.

cutaneous and corneal inoculation were refractory to cutaneous and corneal inoculation, and their serum was weakly virulicidal. Corneal immunity ceased in three and a half months but the skin immunity was still present. It is a question whether the inherited immunity is active or passive. Most observers believe the latter. The differences in cutaneous and corneal immunity are probably due only to the imperfect blood supply of the cornea. The fact that animals immunized by cutaneous vaccination have an increase of antibodies without visible reaction seems to prove a further increase of immunity. The conditions in the human are probably not different and the so-called immunity reaction increases the resistance already present (Sato[1]).

In men the serum of normal subjects, even undiluted, does not destroy vaccine virus, but the serum of those vaccinated at any time previously has an inhibitory effect, though it may be mild in some cases. In vaccination of vaccinated or revaccinated men, even if there is a strong reaction, the antibodies are only slightly increased. An adult vaccinated for the first time, whose blood in the beginning is free from antibodies, shows a slightly antivirulent serum. Antibody formation in men seems weaker and less uniform than in rabbits, and no quantitative variations of immunity can be made out.

Whether the immunity produced by vaccination resides in the blood plasma or the cells, or both, has been the subject of much investigation. Ohtawara[2] agrees with some others that there is an active cellular immunity of the body in general. The tissue cells carry the immunity, receiving the antigen and becoming actively immune. He does not deny a slight degree of plasma immunity.

Schneider (1923) found that serum from smallpox patients or convalescents contained antibodies which, diluted 100 to 200 times, completely neutralized highly potent virus. The production of antibodies increased in the course of the disease and convalescence and was in proportion to the severity of the case. Goerttler[3] found in revaccinated subjects specific antibodies in the serum, increasing in further revaccination without relation to the severity of the reaction. Such experiments strengthen the supposition of a further increase of immunity in revaccination.

Empirical Facts Regarding the Immunity of Vaccinia.—Vaccination produces immunity toward itself at a somewhat variable period. When vaccination is repeated daily, as in the "vaccinization" sometimes used, it ceases to take usually between the fourth and sixth days. By the eighth day in a normal vaccination there is immunity not only to vaccination, but also to smallpox. Exceptions to this made Layet put the period of safety at the ninth day, and Burckhardt the eleventh. Most of the experience regarding the exact period of immunity against smallpox is derived from the early days, when the results were tested by variolation.

[1] Experimentelle Beiträge zur Vaccineimmunität. *Ztschr. f. Immun. Forsch*, Orig. 1921, **32**, 481.

[2] Experimental studies on the process of the vaccinal immunity. *Japan Med. World*, 1923, **3**, 1.

[3] Ueber das Vorkommen von virulizidal Stoffen in Serum Revakz. *Ztschr. f. Immunitätsf.*, 1923, **38**, H. 3.

Sacco got only local eruptions by inoculating smallpox from the eighth to the eleventh day; none at all after that.

It is irrational, however, to fix a definite time for the appearance of vaccine immunity. As in other diseases this varies within certain limits, according to the subject and the intensity of action of the vaccine.

A very important practical question is with reference to *insusceptibility* to vaccination, regarding which there has been much unnecessary difference of opinion. It was known in the period when smallpox was universally prevalent that certain people escaped it. The conditions can hardly be essentially different in vaccination. It is not to be supposed in either case that the immunity is permanent and complete. Illoway published a case suggesting that one part of the body may be immune, and others not, toward vaccination. If we admit, as some do, that there is no such thing as natural immunity against vaccination, we have to ascribe all the failures to imperfections in the lymph or technique and from a practical standpoint we cannot do better than take such ground. The alternative is scientifically well-founded, but can not be positively proved. Few can say, with Cory, that they have made many thousands of vaccinations without a failure, unless the criterion of success is placed dangerously low; but many can recall cases in which several unsuccessful attempts have been made, and then at some later time the patient has taken vaccination or acquired smallpox. According to the careful observations of G. R. Phelps (1923) there may be no reaction in 1 or 2 per cent. of vaccinations even when repeatedly tested with fresh and refrigerated lymph. Some of these subjects have scars, some have none and some may have had smallpox. All run the risk of acquiring smallpox if exposed to severe infection.

Smallpox itself does not render the body permanently immune to vaccination as is proved by numerous cases. It is often assumed that if vaccination takes, the subject would have taken smallpox if exposed; on the other hand, if it does not take the subject is supposed to be immune. Neither conclusion is justified, and the second one has often led to serious consequences.

Congenital or Hereditary Immunity.—Curiously in contrast with the disbelief in temporary insusceptibility to vaccination is the view that has been expressed as to inherited immunity from vaccination of the mothers. There are several sides to this question. In the first place it may be said that vaccination has not been general enough nor perfect enough to account for a large number of immune children. It is often suggested that young infants, according to some up to ten weeks of age, are more or less immune to vaccinia, having been immunized *in utero*. On the other hand, many infants have been vaccinated in the first few days of life and though in some the operation fails, others give perfect results. Mensching,[1] reports 684 vaccinations of new-born children, the latest on the third day, with 70 per cent. of case success and 41.7 per cent. insertion success. In 11 per cent. of cases the failure might have been due either to immunity or to faulty technique, the exact cause not being demonstrable.

[1] Beiträge zur Kuhpockenimpfung, etc., *Arch. f. Kinderhlke*, 1921, **68**, 24.

The course in general was as usual and there was no bad effect on the weight. Of children vaccinated soon after the mothers had been vaccinated 62 gave successful results. Twins were vaccinated, the mother having been vaccinated four days before their birth. Both were nursed by the mother, one had a successful vaccination, the other failed. From the evidence available it seems certain that no practical value can be attributed to intra-uterine immunity.

As vaccine immunity varies in the time of its appearance, so does it vary in duration when once established. This general law, true of all diseases that produce immunity, was often unrecognized in the early days of vaccination, and even now is often overlooked. Failure to recognize it lies at the basis of much of the present-day smallpox, and much of the antivaccination movement. Even in Jenner's time there were those who doubted life-long immunity, some of them putting the time as low as three years. Early cases of smallpox in vaccinated people and early vaccinations were misunderstood, and it was not until revaccination was carried out on a large scale that materials were prepared for such a demonstration as that of 1870–1871.

It is clear that no fixed period can be given for the *duration* of vaccine protection. The ten-year average is probably too long for the individual, but gives good results when large proportions—80–90 per cent.—of the population are well vaccinated. The periods of three months or one year advocated by certain vaccinators are shorter than is necessary for practically complete protection; the seven to nine year interval of Japan is a good one in many respects, though perhaps not better than the revaccination in the twelfth year obligatory in Germany. The success of revaccination varies much in different times and places, a large part of the variation being obviously due to perfection of technique and quality of lymph.

Vaccinated people may acquire smallpox, just as in some cases smallpox occurs a second or even a third time, but they do so in much smaller proportion than unvaccinated. This has been shown so often that it is remarkable that those who oppose vaccination because of its occasional failures do not recognize the fact. The general superiority of the revaccinated German soldiers over the civil population in 1870–71 has been mentioned. This becomes obvious by comparing some figures. The mortality in the army was 3.53 per 10,000; in Dresden, 32.66 per 10,000; in Berlin, 63.26 per 10,000; and in Hamburg 107.5 per 10,000. The total statistics for Germany are most convincing but a few examples must suffice. According to the reports of the Imperial Health Office there were among the 64,000,000 German population in the ten years, 1901—1910, only 380 deaths from smallpox. In Berlin there were 70 cases (not deaths) in seven years, in Cologne 1 in ten years, and in Frankfort 9 deaths in ten years. The cases are most frequently in foreigners, and the cities most affected are those chiefly resorted to by foreigners.

Another well-demonstrated fact is that vaccinated people who contract smallpox have it, on the average, much less severely than others. Huguenin, from the statistics of 62 hospitals, gives the following: Mortality of unvaccinated from smallpox 46.6 per cent., of vaccinated 9.2

per cent. These figures do not apply to other statistics, as both the type of epidemic and the efficacy of the vaccination vary. In St. Louis widespread vaccination of children had been opposed. The majority of children in the public schools are now vaccinated, but those in the private schools are not. Between April 1, 1901, and March 31, 1902, and April 1, 1904, to November, 1910, 195 cases of smallpox appeared among school children; 45 of them had been or were in the public schools; of these 195 only 3 had been vaccinated, none within a recent period.[1]

Striking evidences of the protective value of vaccination have been seen in the Philippines, Cuba, and Porto Rico. In the former, during the Spanish rule, the mortality from smallpox was about 6000 per year. By 1906 over 3,000,000 of the population were vaccinated without a death from the operation. In one place out of a population of 2000, 1000 unvaccinated people took smallpox from an inoculated case and 400 died; 800 were vaccinated; there was no case of smallpox after the incubation stage and no deaths. The other 200 people fled.

Abnormalities of Vaccination.—Vaccination does not always run the typical course (even in primary cases) that has been described. Jenner well understood this and pleaded for a careful training on the part of vaccinators; but this has often been neglected, with disastrous results in many cases.

In all cases in which the vaccine lesion is atypical in course or in the scar it leaves, the operation should be repeated within a period depending largely on the danger of smallpox. If that is present, it is better to vaccinate at once; if not, within six months or a year at most.

An interesting but unimportant anomaly is the appearance of small vesicles near the principal ones about the third or fourth day—secondary vesicles or "vaccinolæ." The writer is convinced they are not always due to accidental inoculation of the surface of the skin, but that they arise from germs transported in the skin. They are not uncommon in vaccinated calves, and recall the distant eruption in natural or inoculated smallpox. They do not necessarily indicate a strong or active specific germ, but in calves often follow inferior lymph. Nobl explains them by delayed formation of antibodies.[2]

Incidental eruptions have been noted from the beginning of vaccination. They depend upon the same general causes as other similar skin manifestations, and require a certain bodily predisposition. They have various types roseolar, resembling the rashes of measles or German measles, or more diffuse like that of scarlet fever; or they are urticarial or like the various manifestations of erythema multiforme. Most of them begin near the seat of inoculation, but the erythematous form has a special predilection for the extremities, and the urticarial variety may involve the mucous membranes, as the bronchi. These two forms may begin as early as the second day; the more superficial eruptions usually late, from the seventh to the tenth. Minute vesicles sometimes occur at the height of the rash, and pigmentation with degeneration follows.

An anomaly of some importance is the *hypertrophied scar* that some-

[1] *Interstate Med. Jour.*, 1912, **19**, No. 2.
[2] *Ztschr. f. Kinderheilkunde*, 1912, orig., Band 4, p. 427.

times follows. It may occur even after a typical and uncomplicated lesion. Red at first, it finally becomes pale. It is rather hard, involves the true skin, resembles a keloid in appearance, but usually disappears very slowly, and thus is free from the most important characteristic of true keloid, which, however, sometimes occurs in the negro. In some cases a growth of hair is stimulated around the scar.

Generalized vaccinia is a term that has been applied to conditions not always the same. Strictly speaking it should be applied to cases in which a widespread eruption appears on the body, with the anatomical and infectious characters (inoculability) of the primary vesicle. Most of the cases reported under this name have been eczema or other skin disease in which vesicles or pustules have occurred in larger or smaller numbers. In some it could be demonstrated that multiple infection had occurred from scratching. In many the lesions were not characteristic in course, through they were in anatomical features. Henoch emphasized the close anatomical resemblance of certain eczematous and accidental eruptions to vaccinia and variola. In a few cases there was a widespread infection without a previous skin disease. Martin reported one in which a calf was successfully inoculated from the contents of some of the vesicles, and from the calf in turn a number of children and an adult. Groth reports a case and states that from 1885 to 1900, out of 2,285,579 vaccinations in Bavaria there were 50 to 60 cases of generalized vaccination. As Malcolm Morris said, the remarkable thing about generalized vaccinia is that it is not more frequent. The prognosis is good in simple cases; bad in those depending upon an eczema.

Accidental vaccination and autovaccination are not very uncommon. They are likely to occur from scratching of the vesicle, though they have often been produced by infection from one person to another. In many cases the genitals have been the seat of the secondary vesicles, often producing, especially on the vulva, lesions that may give rise to much difficulty in diagnosis. The same difficulty often arises when the vesicle is in other parts of the body. Kite (1923) reported a case mistaken for anthrax. Another common seat of accidental vaccination is the face. Mucous membranes in various localities have been involved. A common and very important locality is the eye, either in the conjunctiva or the cornea, which was fatal in a case reported by Dietter. Blindness has followed, and in 9 out of 61 cases there was more or less disturbance of vision. Toomey (1922) in reporting a case of accidental vaccination of the cornea calls attention to the danger from splinters of glass in breaking the vaccine tube. Previous vaccination in such a case would give no protection to the cornea because even slight anaphylactic reaction might cause permanent injury.

Accidental vaccination of the nose is perhaps more frequent than the reports indicate. Lublinski gives 4 cases, 1 original. An interesting location was the tongue, in a mother who sucked the virus from her child's arm. Physicians have inoculated their lips by blowing through vaccine tubes. The ease with which infection can take place is shown by a case in which a physician who dressed a child's arm infected the mother by a local examination. An important contribution to the sub-

ject is that of the zoölogist Blochmann,[1] whose own child was severely injured by vaccination.

Complications.—They may be considered with reference to their mode or origin or to their anatomical or clinical peculiarities. Inasmuch as the same sort of lesion may arise either from infection with the vaccine or later, it is more convenient to follow an anatomical-clinical classification.

Relapses with characteristic lesions have been reported some weeks after successful vaccination. They recall the relapses of smallpox reported in the days of inoculation. Both accidents indicate that disposition is not exhausted, the virus being relatively too strong or immunity too weak.

Anaphylactic symptoms are rarely seen after vaccination. Carl Wagner (1919) reported a case with œdema of the body, pallor, dyspnœa, slow pulse and weakness in a hay fever patient. He also reports 5 cases with anginal pain.

Vaccinal ulcers may resemble the anomalous ulcerating form but differ in that they may occur after the vesicle has made a typical beginning. They are especially likely to occur when poor virus is used, but may follow good vesicles which have become infected. Anemia and cachectic conditions are predisposing causes. The ulcers are indolent, with flabby and sometimes exuberant granulations. Glandular complications are not always present. Extensive loss of tissue may follow, with large and deformed scars. If the complication comes on after the vesicle has reached maturity some protection is probably given, but unless the operator is satisfied as to the course, the vaccination should be considered a failure. A number of deaths have followed this complication.

Postvaccinal gangrene can not be sharply separated from the preceding. As Vollmer (1921) points out, it may be due to oversensibility of the skin, abnormal condition of the lymphatics or accidental septic infection. There is another form of gangrene, called *vaccinia gangrœnosa* by Hutchinson, in which multiple eruptions occurred on the eighth day, surrounded by an areola, in which gangrene developed, with death in the second week. Such cases appear to be much less frequent now than formerly. It is probable that in some cases scurvy or some purpuric affection was present.

Hemorrhagic diathesis sometimes first shows itself after vaccination, but purpuric conditions seem less frequent in vaccination than in smallpox. There may be fatal hemorrhage from the incision. Similar hemorrhages have been observed after vaccination in leukemia. Doré reported (1922) a case of hemolytic icterus. In all hemorrhagic cases the prognosis is serious.

The most important infectious complications of vaccinia are the *pyogenic diseases*, including *erysipelas*. These are much less frequent than when humanized lymph was used and when instruments were never cleaned. Erysipelas may occur at any stage of vaccination and is spoken of as early or late, according to the period. It sometimes occurs so early

[1] "Ist die Schutzpockenimpfung mit allen notwendigen Kautelen umgeben?" *Tübingen*, 1904.

that we must look upon the operation or the lymph as the exciting cause. In most cases it occurs in the second week. The areola is evidently an erysipelatous lesion but its relationship has not been sufficiently worked out. In most cases there is a distinct history of rubbing or scratching and obvious uncleanliness. The disease has occurred in epidemics, due to some fault in lymph or operation, at other times with epidemic erysipelas of other parts of the body. The latter possibility is ground for an important objection to hurried vaccination during epidemics, which often occur at a season favorable for erysipelas, instead of formal vaccination at a more favorable time of year.

The local and general phenomena are those common to erysipelas in any part of the body. The prognosis depends upon the condition of the patient, and the severity and extent of the erysipelas. Unless the complication comes on very late the vaccine vesicle is checked in its development and immunity is not produced. In any case the lesion is infected, ulcerates, and an atypical scar is the result.

Abscess, furuncles, lymphangitis, cellulitis, and *phlebitis,* suppuration of axillary glands, and *pyemia* are rare but serious complications that need no special description. *Suppurative parotitis* is a rare occurrence after vaccination. In all the pyogenic complications it is important to treat the conditions according to the general and special rules that apply to such diseases in any part of the body, and never to neglect or even temporize with them in the belief that the vaccination may suffer. This must be considered a failure in all cases in which the vaccine lesion is involved early, or where its course is altered.

An interesting and important complication is *contagious impetigo,* which sometimes occurs in recently vaccinated people as it does in others. "When due to the vaccine, the cases develop in groups. The vaccine vesicles become pustular, itch severely, rupture early, and infect the body in many places." Voigt mentions a small epidemic following arm-to-arm vaccination from a healthy child, on the eighth day. In many cases the infection is accidental. *Pemphigus* is a much rarer complication, sometimes difficult to distinguish from impetigo. Erythema multiforme, E. iris, and other varieties to E. bullosum, occur in rare cases several weeks after vaccination, with the scab, sometimes obviously infected, still present. In these, as in all cases of anomaly of the lesion with accidental infection, early antiseptic treatment should be used.

Eczema, psoriasis, and various other chronic skin diseases, sometimes follow vaccination, especially when the operation is done in hot weather. In the majority the skin diseases are already present, not noticed or not brought to the attention of the physician, and then any increase in severity is ascribed to the operation. In all vaccinating the physician should ascertain the existence of a skin disease, and either not vaccinate at all, or, in case of danger of smallpox, try to vaccinate in sound skin. In such cases a light but efficient bandage may be used.

Herpes circinatus is a rare occurrence after vaccination, explained by infection with *Trichophyton tonsurans,* a common parasite of cattle.

Measles, scarlet fever, and other acute exanthemata sometimes occur in the course of vaccinia without causing any serious effect on each other.

Jenner noticed that both measles and scarlet fever caused a suppression of the areola, which reappeared after the other exanthem faded. There is no proof that *epidemic encephalitis* has any relation with vaccinia.

Simultaneous Vaccinia and Variola. It was early observed that smallpox and vaccinia could exist at the same time in the body, and though some assert that in such cases the variola is modified, others say, and more accurately, that the severity of the smallpox depends partly on the period at which the vaccinia is introduced. Considering the close relationship of the two diseases, it is easy to understand that they can develop together, and that the immunity of one will check the growth of the other. The situation is not unlike that which exists when vaccine is inoculated on successive days. All the lesions may develop together until immunity is set up by the earliest, and then all subside.

Huguenin describes the chief possibilities with smallpox as follows:

1. In case vaccine is inoculated just before or during the primary fever of smallpox the latter proceeds uninfluenced, unless there has been a previous vaccination. The vaccine, however, fails because of the immunization of the body by the variola.

2. If the vaccination is made at the end of the stage of incubation of variola, both infections may go on side by side.

3. If the vaccination is made in the middle of the incubation of variola, the eruption of the former will occur two or three days before the primary fever of the variola. Only a mild smallpox or a varioloid develops.

4. If the vaccination is made in the beginning of the incubation stage of variola, the difference being six to eight days, the variola will be abortive.

5. In the first day of the incubation, vaccination prevents the smallpox, though there may be fever.

6. If a child in an infected house is vaccinated before it is infected, there will be no symptoms of smallpox.

There are some exceptions. The variola may proceed unaffected by vaccination, which may not develop until after the smallpox has run its course. Vaccination and smallpox may occur simultaneously, the latter retarded but not rendered abortive. The vaccination may develop imperfectly and the variola run its course and even result fatally. In view of the great number of more favorable cases, such accidents should not prevent vaccination in every case in which infection is threatened. In the first three days after infection, even in the fourth or fifth, careful vaccination should be made in at least four places. In such cases, especially if the type of variola is severe, one may with advantage practise successive vaccination every day until the eruption becomes vesicular.

Syphilis is not to be considered as a possible complication if bovine lymph is used, except from extraordinary carelessness on the part of the operator or the patient.[1] The same may be said of *leprosy*, which has in rare instances followed arm-to-arm vaccination in leprous regions. Leprosy bacilli have been found in the lymph of vaccine vesicles in lepers (Arning and others). *Tuberculosis* has only historic interest in connection

[1] Nobl (1907) showed that vaccine lesions in actively syphilitic cases do not contain spirochetes.

with vaccine, though it will always be important for propagators of vaccine. Howk and Lawson (1920) found that tuberculosis in any stage or any degree of activity was not affected favorably or unfavorably by vaccination.

Tetanus has a remarkable history in connection with vaccination. It is so rare in general that only 7 cases could be found in the Index Catalogue, and McFarland could find only 15 altogether in the literature up to 1899; yet he was able to collect 52 cases reported more or less completely, and to learn of 28 more not well authenticated, after that date. Since then a few cases have been reported. McFarland found that: (1) Tetanus is not a frequent complication of vaccination. (2) The cases occur in small numbers after the use of various viruses. (3) An overwhelming proportion occurred after the use of a particular virus. (4) Tetanus bacilli may be present in virus in small numbers, derived from manure and hay. (5) Through carelessness or accident the number may be greater than usual. (6) Avoidance of the complication is to be sought in greater care in the preparation of the virus.

Reading the accounts of separate cases, and still more those of epidemics of complications, gives one an unfavorable view of vaccination Three things must be considered in this connection. We no longer, thanks to vaccination, see or suffer the horrors of pre-Jennerian smallpox with its complications. Nothing else would have removed these so effectually as has vaccination. In the second place, many of the accidents —almost all of the severe ones—are avoidable. Moreover, we need to take a broad survey of vaccination in order to get the real proportions. This has been admirably done for us by Voigt, for thirty years director of the Hamburg Vaccine Institute, having probably the largest vaccine territory in existence. In this time 400,000 persons were vaccinated in the institute; in the whole district, nearly 600,000 in twenty years. Out of 589,586 school children vaccinated and revaccinated there were: Inflammatory complications, probably chiefly due to staphylococci, 35; 2 fatal. Erysipelas, 13; 2 fatal. Phlegmon, 4; 2 fatal. None of the pyogenic cases were due to the operation itself. Eczema, 293, 85 of which began before the vaccination. Urticaria, 32 cases. Impetigo, 85 cases, 50 of which were not due to vaccination. Tetanus, 1 case, recovered; this began on the fourth day, several days after the patient had fallen upon his head.

Another useful series of data is the following:[1] In Germany in thirteen years, 1885–97, 32,166,619 children were vaccinated; 115 of them died within a few weeks or months after the operation, from injuries presumably due thereto. This gives a mortality of 3.5 per million. In 67 cases only, however, was it probable the injuries were due to vaccination. In 1902 there were no deaths traceable to vaccination, but 2 from subsequent invasions. As the report says, *compulsory school attendance is far more dangerous than compulsory vaccination.*

At various times vaccination has been thought to have a curative effect upon other diseases. Most of them are diseases in which it would

[1] *British Med. Jour.*, April 16, 1904, p. 903.

be difficult to prove the exact relations, such as whooping cough, leprosy (Rake), tuberculosis (Winogradoff), and various skin diseases. Hypertrophic scars, such as sometimes follow vaccination, and nævi seem more promising. In such cases superficial scarification and vaccination with lymph of good quality would seem justifiable.

The Practical Application of Vaccination.—There is a remarkable discrepancy between our knowledge of vaccination and its benefits, and the practical application of this knowledge for the prevention of smallpox. Errors of technique and exaggerated ideas of vaccine immunity have been partly responsible for the neglect of and opposition to vaccination; but, though we still need further information concerning many details, we have enough to warrant a much wider use of vaccine than now exists in many countries. It is certain that vaccination applied to the fullest extent, and repeated once or twice in the age of greatest predisposition, has almost abolished smallpox whenever it has been tried. Nothing else has done this and the experience of every locality that has tried to get along without vaccination, depending upon sanitation alone, shows that until our ideas of smallpox are radically changed we are not likely to get a satisfactory substitute for vaccination.[1]

The continued existence of smallpox, often in epidemic form, makes more obvious the need of improvement; for, even when the disease is mild it causes far more deaths, more alarm, and more suffering than vaccination ever has, and, moreover, there is no reason to think that the type will remain permanently mild.

It seems expedient to consider some of the reasons for imperfect vaccination and the possible means of improving the condition.

1. There is no order, system, or uniformity about the operation. The result of this is that large numbers of people of all ages remain unvaccinated, usually because they know no better. This furnishes so large a proportion of predisposed subjects that smallpox once introduced is sure to obtain a foothold, and in the epidemics that result even some vaccinated people get the disease and some of them die. The proportion of unprotected people varies in different parts, but in rather large series of cases the writer has not found a greater proportion of the population than 60 per cent. that showed scars from vaccination, and most of these scars were unsatisfactory. In recent years among selected subjects, such as college students and men in military or naval service, a larger proportion of good scars can be found. The limitation of a single vaccination and even of revaccination on the one hand, the great danger of smallpox on the other, and the advantages of widespread vaccination, make the subject not one of individual complaisance, but one that should come under the sanitary control of the authorities.

2. Systematic revaccination, an essential part of the process, is even more neglected. Carried out as it should be, it would make still more certain the protective influence of vaccinia, and so lessen the number of possible foci of variola.

[1] Dock, Smallpox Quarantine and its Failure in Practice, *Jour. of the Missouri State Med. Asso.*, January, 1912. An account of an epidemic in which a militia company was used, without success, to keep smallpox inside an asylum.

3. No sufficient provision is made for the production of safe and trustworthy vaccine virus. Past experience has shown that the private manufacture of vaccine opens the way for a greater degree of carelessness than should be permitted in such an industry. Inspection of establishments for the production of vaccines and analogous preparations is made under a United States law. The establishments are inspected and the methods of manufacture, construction, and administration investigated. Samples of vaccine are examined, and, if there is any reason, the yearly license is revoked or suspended. The value as well as the need of such inspection is best shown by the fact that within a year of the beginning of the work, four establishments were refused licenses, and others were obliged to improve their methods, rebuild laboratories and barns, etc. There was also improvement as regards bacterial contamination of vaccine.

Unfortunately, the tests as to the specific activity of the virus are so far insufficient, and much of the vaccine used is seriously weak. Regular vaccination at fixed periods would add much to the certainty of securing good vaccine, because makers could prepare for the demand, and the virus would not suffer, as it does now, from insufficient ripening or from being kept too long after it is ripe.

4. There is no way of being certain the operation will be well done and the result accurately recorded. In many places local or State laws provide for compulsory vaccination, but this can be and is evaded in many ways. "Internal" and other fraudulent methods are practised, and false certificates are given by legally qualified but unprincipled practitioners who object to vaccination. Mothers suck out the virus as soon as the operation is done, and as no inspection of the result is necessary, unfounded security is set up, based upon a fallacious belief of widespread vaccination, inevitably leading to disappointment and to erroneous ideas of the value of vaccination.

For the best results to follow laws compelling vaccination it is necessary to have the active as well as the passive consent of the people, and it is sometimes said that Americans in general would never submit to compulsory vaccination. The writer thinks this is a serious error, and that the chief difficulty is the ignorance of the public as to the desired methods—an ignorance not entirely unconnected with defective laws and still more defective administration. The patience with which, in various parts of the country, the public submits to quarantine, detention, spasmodic and inconclusive vaccination, not to mention the unpunished malpractice of ignorant vaccinators, is the best argument in favor of the view that the population, as a whole, would welcome any wise and conservative law. It is sometimes said that general vaccination would open the way for a series of preventive inoculations for various other infectious diseases, but this is not necessarily so. Whenever it can be shown that any other disease can be protected against as well as smallpox can be by vaccination, and with as little risk, it would obviously be well to take advantage of the discovery.

Before any radical change can be made in our vaccination laws, physicians can do much to bring a better sentiment than exists at present,

and also to improve the practice of vaccination. They should encourage vaccination and revaccination in all persons with whom they have professional relations, and do this not at times of epidemics, but as early as the occasion permits. They should advise and select a time when the discomfort of the operation and the danger of complications is least; that is, in the early summer or early winter, and when there are no epidemics of dangerous contagious diseases, like scarlet fever, measles, diphtheria, croup, whooping cough, or erysipelas.

Parents should be advised to have children vaccinated between the ages of six months and two years, or earlier in case of danger. Children should also be revaccinated when they begin school, especially the public schools, with the danger from the carelessness of other parents. After that revaccination should be practised according to local conditions, without a longer interval than ten years until adult age is reached, and particularly when new occupations offer renewed dangers. For example, recruits, operatives in manufacturing establishments, and those who work in large stores or offices, should be revaccinated. Mail clerks and all employees on trains should be thoroughly revaccinated.

Individuals with serious organic or constitutional diseases, with severe skin diseases, especially those that induce scratching, should not be vaccinated unless there is immediate danger, but the reasons and risks should be clearly stated to the patients, parents or guardians, so that greater precautions may be taken. Revaccination in older people should not be done during the existence of any serious disease, unless there is distinct danger of smallpox. In such cases it should be practised and the wounds carefully observed. During menstruation, especially the early part of the period, is not a good time for vaccination. The writer has seen vaccination and revaccination carried out several times in the last few years on most of the patients in a general hospital, and though some painful swellings occurred, there was no serious damage.

Every effort should be made to obtain good material. The operation should be looked upon as an important one, and sufficient time and pains taken to make it as aseptic as possible. The patient should be told of the necessity of noting the result and of treating any untoward symptoms, the accidental nature of which should be made clear. Records should be kept, as well for the information of the patient as for that of the physician. With the greatest care, however, certain risks are present, and so it is unwise for the physician to force the operation upon those who are unwilling or to give assurances of absolute harmlessness.

CHAPTER III

CHICKENPOX

By E. J. G. BEARDSLEY, M.D.

Chickenpox is an acute infectious disease occurring chiefly in children although occasionally encountered in adult life. It is usually characterized by a slight fever, mild constitutional symptoms, and a skin eruption that appears in successive crops. If the rash is under observation from the beginning, the lesions are first macular, then papular and finally vesicular. The maculo-papular stage is seldom seen by a physician outside an institution as it persists but a few hours and the prodromal and early symptoms are so mild as to seldom attract attention until the characteristic vesicles appear. These soon fill with clear contents, are easily ruptured, begin to dry and shrivel and form granular crusts in from three to five days.

With the exception of German measles, chickenpox is usually the mildest of the exanthemata and, when unaccompanied by complications, is attended by no mortality. Fatal cases have, very infrequently, been reported when the disease was unusually virulent and attacked a child with slight resistance. One attack of chickenpox usually confers immunity for life.

Etiology.—The specific agent has not been identified. Early attempts to induce chickenpox by inoculation were not, as a rule, successful but more recently, Steiner, Smallpiece, Kling, Rabinoff and Michael have reported successful attempts at inoculation. Kling, of Stockholm, believes that inoculation confers protection and states that of thirty-one children inoculated only one contracted the disease, although all were exposed. The method of inoculation is simple. The contents of a perfectly clear varicella vesicle are inoculated into the arm. About the eighth day papules appear at the site of the inoculation, followed in twenty-four hours by typical varicella vesicles. In a few instances a scanty papular eruption appears on the body and this is looked upon as an abortive attack of chickenpox.

The disease is easily communicable but the mode of infection is unknown. Chickenpox occurs chiefly in early childhood, the majority of the cases occurring between the first and the eighth year. Although nursing infants have contracted the disease this is unusual as very young infants frequently escape infection even when intimately exposed. That children under one year of age are not immune is emphasized by the fact that 691 patients under one year of age were reported in the statistics of Basel. In large communities the disease is endemic but as the number of susceptible subjects varies from time to time there are periods when there are so many cases that the disease seems epidemic.

The mildness of the usual attack and the lack of public sentiment for strict isolation and effective quarantine favor the dissemination of the malady. While chickenpox is chiefly a disease of childhood *no age is exempt*. There exists a mistaken impression regarding the insusceptibility of adults. Mature individuals who escaped infection in childhood are susceptible and those who have lived isolated lives in country districts frequently contract chickenpox in adult life. The military experience of the World War provided frequent opportunities to study chickenpox in adult patients. The epidemic studied by Tyzzer in the Philippines occurred entirely in grown people. The Municipal Hospital of Philadelphia treated 51 adults for chickenpox in thirty-two years. Wanklyn states that of 200 patients with chickenpox sent to the diagnosing station in London during the smallpox epidemic of 1901–1902, 16.7 per cent. or 33 cases were over eighteen years of age. Of 6014 cases reported at Basel only 3 patients were over forty years of age, one being over fifty. Schamberg saw the disease in adults 16 times in eighteen months and states that although adult infections are not common they are not as excessively rare as some authorities believe. MacCombie reports having seen a typical infection with chickenpox in a woman, aged seventy-one years, and Stelwagon in a man past sixty. The writer has seen the disease in two physicians, both over fifty.

The Relationship of Chickenpox and Herpes.—There appears to be a relationship between chickenpox and herpes zoster but the relationship is not understood. Bokay, in 1892, reported 9 cases in which chickenpox infection appeared from eight to twenty days after an attack of herpes zoster had affected another patient in the same family or hospital ward and when, apparently, the possibility of infection from other sources could be excluded. There have been similar reports from many observers. Parkes Weber has reported a series of cases and Le Feuvre made an analysis of 50 cases illustrating the singular connection between the two diseases. In his series 41 cases of chickenpox followed herpes zoster within the limits of the usual incubation period, in 5 the herpes zoster appeared in from two to five weeks after chickenpox, while in 4 the two co-existed, typical chickenpox developing in three or four days after an outbreak of herpes. Ker reports that in eighteen months 3 out of 7 appearances of herpes zoster in his wards had been followed by cases of chickenpox, otherwise quite unexplained. Schamberg agrees with Comby who states that herpes zoster and chickenpox are essentially different types of disease. Schamberg considers it possible that the organism which produces chickenpox might, in individual instances, attack one or more ganglia in the posterior roots of the spinal cord and produce herpes zoster. It remains to be proved that the association of the two disorders is anything more than an interesting coincidence.

Pathology.—The anatomy of the skin lesions has been carefully studied by Unna and Tyzzer. The first change consists in swelling of the cytoplasm which precedes the vesicular formation. The changes are superficial, rarely extending below the middle layers of the rete, in this respect differing from smallpox in which the process is most pronounced in the lowest layers and in the papillary body. Unna described the changes of

the cells as ballooning degeneration. The nucleus of a large swollen cell divides by direct division, and this process is rapidly repeated until a large number of nuclei are produced within the cell. The cells often attain large proportions. The nuclei are usually grouped in the centre, often so closely packed together that the apposing surfaces are flattened against each other. Exudation from the vesicles beneath the epidermis rapidly takes place and the fluid finds its way into the degenerated epithelium and separates the cells, forming spaces filled with fluid. The lesion may form from one or several centres, but the various small chambers quickly break into one another and form a single vesicle. The degenerated epithelial cells do not form the rigid septa which are always found in the smallpox vesicle. Cells in various stages of degeneration are found free in the vesicle contents or along its floor. The base of the vesicle in which there is an active exudation is almost invariably concave. The vesicles are usually, but not invariably, unilocular and not umbilicated, although this latter is not always true especially in the later stages when there is a tendency to depression of the top of the drying vesicle. The fluid in the vesicle contains fibrin and coagulates spontaneously when removed. The vesicles usually rupture very easily. Few polynuclear leukocytes are found, either in the corium or in the vesicle, unless infection by bacteria has taken place. Abortive cases without complete vesicle formation may occur. In these there is a marked localized degeneration of the epithelial cells without any appreciable exudation. These lesions appear as reddened, slightly elevated, spots and show microscopically a portion of the epidermis wholly necrotic, with the cells disassociated and hyaline in appearance similar to those in the advanced vesicle.

There are no records of autopsies in uncomplicated chickenpox, so that nothing is known as to the presence or character of internal lesions. It is usual for chickenpox to leave slight but very definite cicatrices, which are characteristic in appearance. They are most frequent on the forehead, chest and back. They produce little deformity and are usually visible only on close examination. They are slightly depressed, a trifle paler than the surrounding skin, and vary in size up to 4 mm. They are due to a very superficial destruction of the corium, involving only the papillæ. The destruction is never so deep as to destroy the sweat glands or hair follicles, hence the cicatrix is seldom foveated. Rarely there are more extensive scars, usually the result of infection of the vesicles by scratching, with resultant small ulcers.

Incubation.—The extreme limits seem to be eleven and twenty-four days, but most commonly the symptoms appear from the thirteenth to the sixteenth day. When the disease is produced by inoculation the incubation period appears to be eight days. During the incubation period there are, as a rule, no evidences of illness. Occasionally, slight disturbances are noted such as loss of appetite, lassitude and symptoms of general indisposition including a mild degree of fever. Of 43 patients studied by Corlett, 19 showed neither premonitory symptoms nor a rise of temperature, in 24 there were mild febrile symptoms, slight anorexia in 20, irritability in 17, lassitude in 10, headache in 4, slight pain in the back and limbs in 2, chilliness in 9, nausea in 4, and vomiting in 2. These

symptoms were of short duration and varied from two to thirty-six hours preceding the eruption. No cases of chickenpox *in utero* have been recorded but MacCombie quotes Hubbard as having recorded a case in which a baby manifested the lesions of chickenpox the day after its birth and another crop of characteristic lesions appeared the following day. The mother was not suffering from chickenpox but her six children were.

FIG. 18

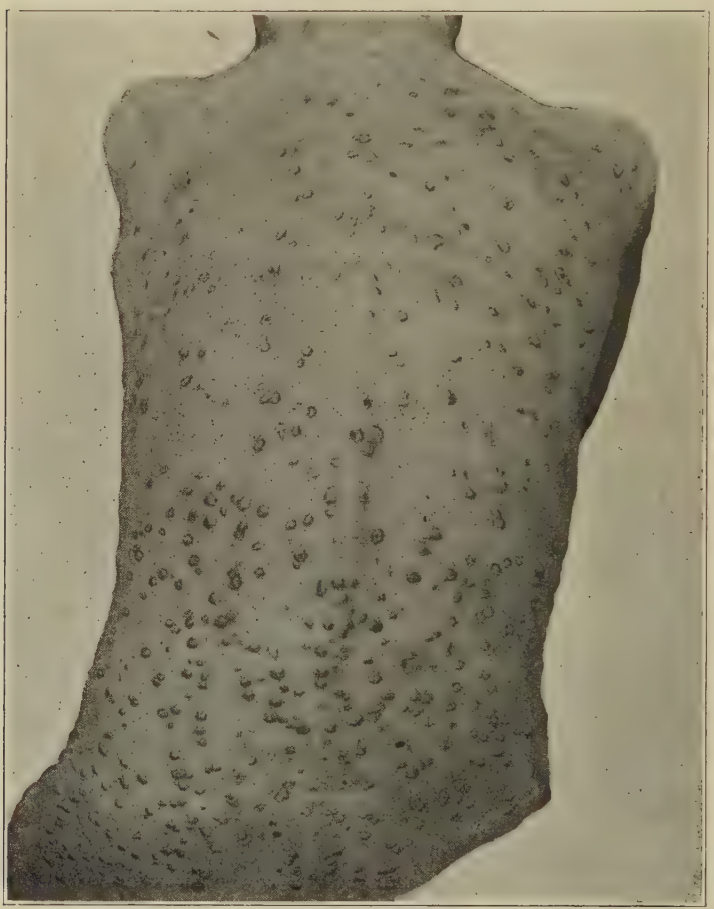
Eruption of chickenpox. The relative frequency of the pocks on the face and body is shown.

In this patient, either the infant contracted the disease *in utero* or the incubation period was one day.

Symptoms.– The appearance of the eruption is usually the first evidence of the disease, especially in young children, but in some patients there are slight and occasionally severe febrile symptoms, with nausea and vomiting. Headache, a feeling of chilliness and general malaise,

followed by moderate and even high temperature are not infrequent, especially in adults and older children. Rarely the initial symptom in a child may be a convulsion accompanied or followed by a sharp rise of temperature which disappears, as a rule, with the full development of the eruption. In young children delirium is not infrequently an early symptom. Pain in the back, arms and legs with headache of intensity

FIG. 19



Eruption of chickenpox.

is occasionally met with both in the stage of invasion and before the eruption is fully developed. Although not common, erythematous rashes sometimes occur both before and at the time of the appearance of the vesicular rash. These vary greatly in appearance, sometimes being urticarial but more often simulating the eruptions of scarlet fever and measles. Ker states that scarlatiniform rashes are not uncommon during

the course of chickenpox. He states that during the stage of invasion such rashes are likely to give rise to errors of diagnosis. They may exist without fever although they are more likely to be seen in febrile patients. The patient may present a more or less uniform flush or an actual punctate rash. The fauces may be inflamed which still further complicates the diagnosis. There is no subsequent desquamation in these cases.

Generally the initial temperature in chickenpox is low, not more than 101° F., higher temperatures are encountered less frequently and in such cases marked nervous and mental symptoms may occur especially in older patients. The temperature usually diminishes and even drops to normal with the appearance of the rash, but if the eruption is very abundant, the fever may reappear or rise again and persist for several days.

Young patients are usually restless and irritable from the itching of the vesicles, which is aggravated by the scratching and rubbing which it is most difficult to prevent. Painful micturition may be caused by the presence of vesicles on the prepuce or on the labia.

The severity and duration of the symptoms depend upon the abundance of each crop of vesicles and upon the number of crops. The lesions which show a tendency to severe inflammation, ulceration and necrosis after rupture determine the severity and length of the illness. In the majority there is little tendency to serious inflammation and the skin heals in a short time but in some patients there is a tendency to swelling and tenderness of the skin, and the formation of impetigenous crusts about the ruptured vesicles. There often are secondary infections due to scratching and widespread suppuration under the crusts, which may result in necrosis of the skin and tissues. The separation of the crusts results in the formation of ulcers which may become extensive and dangerous and muscle is, in such cases, often exposed. In these severe infections it is not unusual for septic erythematous rashes to appear. Scarlatiniform rashes are encountered and, rarely, purpuric rashes make their appearance. When the number of ulcers of the skin and tissues is great the prognosis is very grave as the patients are in an enfeebled condition. When the ulcers are few the patient usually recovers. Very severe scarring frequently results from the large ulcers of the skin and muscles.

Prodromal Rashes.—As previously noted in the symptomatology prodromal rashes are not uncommon although less frequent than in smallpox. The rashes occur, as a rule, during the twenty-four hours preceding the vesicular eruption but may be noted for the first time when the vesicles are first seen. The scarlatiniform rash is the most frequent prodromal rash but morbilliform and urticarial rashes are also seen. The rashes may or may not be accompanied by fever. With a sore throat and a scarlatiniform rash the difficulty of excluding scarlet fever is great. The initial erythematous rash usually disappears with the onset of the vesicular eruption but the former rash may persist for one or more days showing exacerbations with the onset of each crop of vesicles.

The Eruption.—When the eruption can be carefully watched from the beginning, there is a macular and papular stage which precedes the better recognized vesicular stage. The macule persists but a very short time,

rapidly changing into a minute papule which is not unlike the "rose spot" of typhoid fever. The *papule* is pink, slightly raised and its color disappears easily on pressure. It often shows considerable resistance to pressure but does not usually have the characteristic "shotty" feel of the papule of smallpox. Wanklyn has pointed out the fallacy of depending upon such a variable quantity as the "shotty" feel in diagnosis, stating that in many cases of severe chickenpox the papules may be "shotty," especially when located upon the scalp or extremities. The vesicles appear in the central portion of the maculo-papules and rapidly attain full development, the time varying from three to thirty-six hours. The vesicles form so quickly in many instances that they seem to be the first manifestation not only of the eruption but of the disease.

The *vesicles* are transparent, oval or round, although elongated forms with irregular margins are often seen. The vesicle seems to lie *on* the skin instead of being a part of the skin and is often surrounded by a slight, and occasionally a marked, areola of red or pinkish color which gives the lesion the appearance of a large drop of water or glycerine surrounded by a faint red line. The vesicle readily collapses if pricked and the contents are expressed. The erythematous ring usually disappears before the vesicle matures and may be absent throughout. The characteristic vesicle is from 2 to 4 mm. in diameter, projecting 1 to 4 mm. above the surface and is usually not depressed in the centre; occasionally a few vesicles are found late in the disease with slight or even marked central depressions. The contents of the vesicle, early in the disease, are clear and appear transparent beneath the thin covering. As the vesicle matures, if it remains unruptured, its contents become more opaque and, in a few instances, actually purulent. The majority of the lesions, however, have but a short existence, as they are early ruptured by scratching or by rubbing of the clothing. Few remain unruptured for more than two days and these, usually, because they contained little fluid.

The *eruption* of chickenpox generally appears first upon the chest and back, and, contrary to the eruption of smallpox, the body is more affected than the face and extremities. The eruption of chickenpox appears, as a rule, on the covered body surfaces, while smallpox appears on the surfaces exposed to light. On the scalp, forehead, and extremities the lesions may be deeply set in the skin and give a resistant feel similar to that given by a smallpox papule. As a general rule the trunk is most affected; then the face and scalp; the extremities least of all. Vesicles are rare upon the palms and soles although exceptions occur. Lesions on the buccal mucous membranes and palate appear, but the vesicles are quickly ruptured and the lesions usually present the form of slight erosions. Vesicles also appear in the vestibule of the vagina and upon the prepuce and may cause swelling and discomfort. The general duration of the vesicles is from two to three days. They appear in successive crops and the duration of the disease may be a week or even longer. The vesicles may disappear by absorption in which case there will be a very slight scaly crust formed of the dried epidermis, which is cast off and renewed. They are more frequently ruptured and a somewhat thicker crust results due to the presence of dried exudate and deeper necrosis of the epithe-

lium. The crusts are often dark in color and may be made up largely of coagulated blood due to injury of the vesicles by rubbing or scratching. The crusts lie, as a rule, more superficially than those of smallpox, but if the base of the vesicle has been infected the crusts may be set deep in the skin and leave disfiguring scars. A careful search of the body of the average patient will reveal a number of chickenpox scars even when the patient has no recollection of having had the disease.

Hemorrhagic chickenpox is fortunately rare, although it is not uncommon to have a minute hemorrhage into a few of the vesicles. In the severe hemorrhagic forms large and small ecchymoses appear under the skin with smaller hemorrhages into the vesicles. MacCombie states that such hemorrhagic cases are sometimes found in cachectic patients and that hematemesis and melæna complicate the picture.

Complications.—In the usual attack there is little to be feared from complications, as the majority of the patients are but slightly ill and soon recover. There is always the possibility of certain complications. *Gangrene of the skin* is rare. Hutchinson referred to it as "varicella gangrænosa," and Crocker and others gave excellent descriptions. It occurs after the rupture of the vesicles and is apparently caused by secondary infections. Children in poor health and in unhygienic surroundings are most likely to develop this complication. *Impetigo varicellosa.* Welch and Schamberg called attention to frequent infection of the chickenpox vesicles by impetigo and termed the resulting lesions "impetigo varicellosa." *Boils and abscesses.* Although far less frequent than in smallpox, boils and abscesses occur during convalescence from chickenpox. Their usual site is the head and neck. *Erysipelas.* It is strange that erysipelas is not a more frequent complication. Holt reported three fatal cases.

Parotitis has been reported occasionally. Brunner reported a double parotitis with suppuration and I reported an instance in 1909. *Thyroiditis* is another rare complication. Allaria reported an instance in which the gland suppurated. *Otitis media.* As in all other acute infections in children, otitis media may complicate chickenpox. Moy reported 17 instances among 875 cases. *Mastoiditis, meningitis* and *brain abscess* have resulted from otitis media during chickenpox. It is questionable whether the chickenpox infection had any real relationship to these complications. *Laryngitis.* In severe attacks laryngitis is not uncommon. Marfan and Halle reported an instance in which it was necessary to perform tracheotomy, the child making a good recovery, and in another case death resulted, apparently from exhaustion; the autopsy revealed a small ulcer on the posterior surface of one vocal cord, probably the result of a varicellous lesion.

Bronchitis and bronchopneumonia, although unusual, occur in debilitated children and *pleurisy* is also encountered. The fatal cases are nearly all complicated by a bronchopulmonary infection. *Pulmonary tuberculosis* is said to be a sequel in anæmic, debilitated children. It would be nearer the truth to state that children with latent forms of pulmonary tuberculosis frequently contract chickenpox and during the convalescence from this disorder the pulmonary infection is sometimes

discovered. *Endocarditis* is similarly reported as a sequel. The relationship of the two disorders is, probably, accidental. *Synovitis, arthritis and periostitis* have occurred during convalescence from chickenpox. Suppurating joint lesions, though rare, are occasionally reported. *Encephalitis, meningitis, paraplegia, monoplegia*, etc., have been reported as complications. D. C. Wharton Smith, in 1915, reported a case in which acute myelitis occurred two weeks after an attack of chickenpox. As in many of the other complications it is difficult to decide whether the complication is not a coincidence rather than having a direct relationship to the original disease.

Albuminuria and Nephritis.—Albuminuria is frequent in carefully studied cases. The reason that it is not more frequently reported is that urine examinations are not often carefully made in mild cases of chickenpox. Nephritis is a dangerous complication when the affected child is not in good health. Children with other complications, suppurative conditions, particularly, are prone to develop nephritis. Although this may arise during the first few days of the illness it is more likely to appear as a sequel during the decline of the eruption or after the eruption has largely disappeared. A number of fatal cases, complicated by nephritis have been reported. The majority of those affected do not die but a certain proportion develop chronic nephritis.

Diagnosis.—Chickenpox must be differentiated from the manifestations of smallpox, impetigo contagiosa, dermatitis herpetiformis, pemphigus, vesicular and pustular syphilitic eruptions, molluscum contagiosum, acne and herpes. The most important diagnosis is concerned with identifying atypical cases of chickenpox and smallpox. A full discussion of the differential diagnosis of these diseases will be found in the article on smallpox. The chief differential points are as follows:

1. A history of direct exposure to either disease.

2. The vaccinal condition of the patient. Successfully vaccinated patients, especially children and more especially if the successful vaccination is of recent origin, are extremely unlikely to have smallpox.

3. The eruption of smallpox is almost invariably preceded by two or three days' illness with characteristic and frequently severe symptoms. Illness of a severe nature preceding the eruption of chickenpox is rare and especially rare in children.

4. The constitutional symptoms are much less marked in the usual case of chickenpox and one rarely encounters chickenpox in an adult with severe initial symptoms and profuse and misleading eruption.

5. The characteristic distribution of the lesions in the two diseases is quite different. In smallpox the uncovered portions of the body, show the greater number of lesions, while in chickenpox the trunk, especially the back, is most affected. Rarely the lesions of chickenpox appear upon the soles and palms but never in such number as in smallpox.

6. The eruption of chickenpox appears in crops on successive or alternate days and the lesions are in all stages of development; in smallpox the lesions usually exhibit uniform development.

7. The histology of the skin lesions is different, chickenpox showing the formation of epithelial giant cells which are absent in smallpox; the

chickenpox vesicle has a single chamber while that of smallpox is multiple. The epithelial cells in smallpox contain cytoryctes and these bodies are absent in chickenpox. Even the microscopic examination of the contents of the vesicle may be decisive, for the presence of the large multinucleated epithelial cells strongly favors the diagnosis of chickenpox.

From *impetigo contagiosa* it is sometimes difficult to distinguish chickenpox. A history of direct exposure to either disease is helpful. The lesions of impetigo are chiefly upon the face and hands but in some cases they may appear over the body. The fact that chickenpox lesions appear in crops is, frequently, an aid. The finding of a typical varicellous lesion in the roof of the mouth is suggestive, as impetigo does not affect the mucous membranes.

The lesions of *dermatitis herpetiformis* may appear very similar to those of chickenpox, although it is unusual to find typical oval forms in dermatitis herpetiformis. The skin disease exhibits a marked tendency to recur, and thus a history of previous attacks is helpful. In the early stages of *pemphigus* when small bullæ are present such lesions may be mistaken for chickenpox but when the large blebs appear the diagnosis is evident. Vesicular and pustular *syphilitic* eruptions occasionally cause difficulty but with a correct history and a Wassermann test, few errors occur from this cause. In *molluscum contagiosum* the small tumor-like bodies are not transparent and are filled with soft granular substance easily expressed from the lesion. There is not likely to be fever while in chickenpox with a large crop of lesions slight fever is common. *Acne* very infrequently causes difficulty if a correct history is obtained and the lesions are examined in a good light. *Herpetic eruptions* may resemble chickenpox lesions but a magnifying glass reveals the minute vesicles of the herpes.

The most important and the most difficult diagnosis is between a very mild form of smallpox and a severe attack of chickenpox. The differential points mentioned above usually aid in making a correct diagnosis, but there are cases in which at a given period and in the absence of a complete history a correct diagnosis may be impossible. In such a case it is frequently useful to vaccinate the patient against smallpox and await developments. If the patient has smallpox the vaccination will not prove successful while if the disease is chickenpox and the patient is not protected by vaccination against smallpox the successful vaccination is an excellent diagnostic feature.

Prognosis.—In an uncomplicated case in a patient not exhausted by other diseases the prognosis is invariably good. If the patient is attacked by chickenpox during convalescence from some prolonged and severe illness, such as scarlet fever, pneumonia, or diphtheria, death may result. In such cases there seems a distinct tendency for the varicellous lesions to become gangrenous. Erysipelas may appear during convalescence, due to infection of the lesions through scratching, and has caused death. Cellulitis and abscess formation have resulted from trauma to the lesions by scratching. In delicate children with little resistance such complications may be dangerous. Nephritis appearing during an attack is not uncommon and I have seen four instances of this complication. Albuminuria is frequent but usually disappears in a few days.

Treatment.—The patient should be isolated or at least removed from contact with susceptible persons. There is a difference of opinion whether healthy children should be deliberately exposed to infection with chickenpox when one child is ill with the disease. I feel that when a child is in good health it is quite as well to deliberately expose it to this infection in early life, as there is practically no danger from the disease or complications if certain precautions are observed. If the disease is escaped in early life the patient is likely to contract it at a more awkward and inconvenient time; an attack in adult life is almost invariably more severe than in childhood. In weakly children or those suffering with or convalescent from prolonged illness it seems dangerous to expose them to an infection even as mild as the usual attack of chickenpox.

Rest in bed in a well-ventilated room with a low diet seems the best rule to follow, at least when the patient has fever. In afebrile patients the usual diet can be allowed. Sometimes there are so few symptoms that it is difficult and even unwise to keep children in bed. The finger nails should be cut short to prevent scratching and when necessary the wearing of mittens or some protective measure must be adopted to prevent the lesions being so scratched as to produce scars. Local treatment to prevent and relieve the irritation and itching is the most necessary part of the treatment. Welch and Schamberg recommend the following lotion.

℞—Acidi carbolici	♏xxx–	ʒj	2–4 cc.
Glycerini		ʒj	4 cc.
Spts. vini rect.		ʒiv	15 cc.
Aquæ qs. ad		fl℥vi	180 cc.

The addition of 10 gr. of thymol or menthol to this mixture aids in allaying the itching but frequently, children dislike both the odor and the cooling sensation caused by these substances. When the vesicles become distended with cloudy material, particularly when located upon the face, it is well to evacuate the material and cleanse the lesions with a mild antiseptic lotion. The following ointment is useful in aiding to prevent secondary infection:

℞—Acidi carbolici		♏x	0|6 cc.
Hydrargyri, chlor. mit.		grs. xv	1|0 gm.
Pulv. amyli,			
Pulv. zinc. oxidi	āā	ʒij	8|0 gm.
Petrolati		℥ss	16|0 gm.

If the patient suffers from a severe skin irritation a dusting powder of boracic acid, zinc oxide and starch, in equal parts, is useful in making the itching less.

In the later stages, where there is crusting of the exudate of the lesions, zinc oxide ointment or cold cream is soothing. Zinc ointment aids in healing the skin lesions after the scabs or crusts are removed by hydrogen peroxide or an alkaline tub bath. Should gangrenous areas appear it is particularly necessary to see that the patient receives special nourishment, plenty of sunshine, if possible directly upon the lesions, and stimulants when necessary.

CHAPTER IV

MEASLES—RUBELLA—THE FOURTH DISEASE—ERYTHEMA INFECTIOSUM—MUMPS

By JOHN RUHRÄH, M.D.

MEASLES

Definition.—Measles is a specific infectious disease characterized by extreme contagiousness, fever, catarrhal symptoms, both prodromal and during the height of the disease, a characteristic early eruption in the mouth—Koplik spots—and later by a characteristic enanthem, exanthem, and a branny desquamation during convalescence.

Etiology.—At present measles is the most widely spread infectious disease, as it is found over the entire world uninfluenced by climate or weather except that it is slightly more prevalent in cold weather, probably due to people being more crowded together. The disease is always present in the larger cities, but from time to time epidemics occur, and these are the result of increased virulence on the part of the disease or of lessened resistance on the part of the inhabitants or in some instances to a new set of children having grown up. From time to time measles occurs as a pandemic. *Susceptibility* is very great but seems to vary from time to time as individuals may be exposed in one or more epidemics and not contract the disease and then be infected by a subsequent exposure. As few persons escape infection altogether, we may assume that but very few are entirely immune.

Measles is transmitted by direct contact in nearly every instance. While it may be possible that the disease can be transmitted by a third person or by fomites, the time which elapses from the contact with the infected person must be short. There seems to be little or no danger of contracting the disease from apartments previously occupied by measles patients, and there are numerous instances in which families with susceptible children have moved into rooms in which measles patients had been living and there was no infection. If five days have elapsed, rooms may be regarded as perfectly safe. The disease is most frequently transmitted through schools, and the child in the preëruptive stage can transmit the disease to an enormous number of others, which explains the outbreak of a large number of cases on nearly the same day. Childrens' parties are another frequent source of infection, and in hospitals and asylums outbreaks frequently follow the admission of a case of measles in the preëruptive stage.

The disease apparently can be carried a short distance through the air, and it is well-known how difficult it is to isolate measles patients unless a separate open air space intervenes. Instances have been reported

where a child has taken measles from a patient on the other side of the ward after an exposure as short as half an hour, with no apparent means of the disease having been transmitted otherwise than through the air. In Grancher's wards, in Paris, where special studies were made to determine the transmissibility and the possibility of preventing its spread, it was found that the infection of measles could be reduced two-thirds but could not be prevented altogether. It would seem that the contagion varies in virulence, some epidemics being very widespread and others more or less limited under essentially the same conditions. The disease may be transmitted from the time of the first catarrhal symptoms, and possibly before, and until the disease reaches its height. The infectiousness is very marked early and is probably greatest about the time the eruption is coming out. When the eruption begins to fade the danger of transmission diminishes, and during the stage of desquamation the danger of transmitting the disease is slight, if there is any at all. The infectiousness apparently disappears five days after the appearance of the eruption. Nursing infants, especially under five months of age, enjoy a more or less perfect immunity and although closely associated with measles patients do not always contract it. Indeed, instances have been reported where the infant sucked the breast of a woman with measles without infection. After about one year of age the susceptibility is great and the non-susceptibility of older individuals is explained largely by the immunity which they have acquired through having had the disease.

The *immunity* caused by measles is complete and lasting and second attacks are very rare. The writer has seen one instance of a child having two attacks five years apart. Congenital measles has been reported a number of times, and a pregnant woman who contracts measles may communicate the disease to her unborn child. The child may be born with the rash in the same stage as that of the mother or in the catarrhal stage and the rash may come out later.

Inoculation Experiments.—Hektoen transmitted the disease by injecting the blood from a measles patient into a young man who had never had the disease. On the thirteenth day there was a temperature of 103° F. and on the following day the eruption appeared. There were no catarrhal symptoms in this patient. In a second case, symptoms began on the eleventh day and the eruption appeared on the fifteenth. Anderson and Goldberger and others have succeeded in transmitting the disease to the Rhesus monkey by taking the blood from a patient just before the eruption appears. They also were able to transmit the disease by using the nasal and buccal secretion, but not by means of the desquamating epithelium. Up to the present time no organism has been described. The virus of the disease is filterable through the finest filters, is easily destroyed by heat, but resists lower temperatures.

Pathology.—The toxemia of measles rarely causes death and the fatal cases are always complicated with other lesions, the most frequent being pneumonia, colitis, and nephritis. The changes in the mucous membranes and the skin are the most striking features. Unna described the changes in the skin as a spastic condition of the bloodvessels. The

ducts of the sweat glands are œdematous and the lymphatics distended, but there is no cellular exudate. There is no mitosis during the inflammatory stage, but karyokinesis may be demonstrated during desquamation. Catrin described the changes as an infiltration of the skin with a sort of colloid material which eventually leads to coagulation and subsequent desquamation. Others describe somewhat similar changes and include cellular infiltration as well. The changes in the mucous membranes are of the nature of a catarrhal inflammation which may affect any part of the body, but the most marked changes are in the conjunctiva, mouth, throat, larynx, trachea, bronchi, and lungs. Focal necroses have been described in the liver.

Incubation.—Symptoms appear from nine to eleven days, and the rash quite uniformly on the thirteenth and fourteenth day after infection.

Prodromal Eruptions.—The prodromal rashes of measles have received but scant attention. Thursfield called attention to a scarlatiniform and sometimes to a papular rash appearing about twenty-four hours before the regular eruption. J. D. Rolleston made a careful study of this subject and found prodromal rashes in 30 cases or 42.8 per cent. of all observed. The prodromal rash is most frequently a blotchy erythema or scarlatiniform rash. It is usually seen on the trunk, behind the ears, or on the extremities, although occasionally it is noted on the face or neck. The rash is always transient and there is no evidence of irritation.

Symptoms and Course.—After infection there is an incubation period in which there are no very apparent changes, the general health is good and the child does not complain. A loss of weight begins on the fourth or fifth day after infection, according to Meunier, and there is a leukocytosis during the incubation. Slight changes of temperature have been observed but are not constant and there is no reason to believe that they are of necessity a manifestation of the incubation period. Sometimes there is malaise, depression and drowsiness. The tentative diagnosis during the incubation period must rest upon the history of exposure, a loss of weight, and a leukocytosis.

The symptoms may be divided into three stages; the period of invasion or the catarrhal stage, the period of the eruption, and the period of desquamation.

The period of *invasion* is ushered in by numerous symptoms which make the diagnosis probable if there is a history of exposure. About the ninth and tenth day after infection, the child becomes listless and drowsy, and the drowsiness is such a constant feature as to be regarded by some as almost pathognomonic. The appetite is poor or lost. If the child is old enough to describe the symptoms there is complaint of headache, a chilly sensation, and of feeling tired. There may be slight or high fever and on this or the following day marked *catarrhal* symptoms appear. The conjunctivæ become congested and slightly reddened. There is coryza with sneezing, the throat is slightly reddened, and there is some cough and often hoarseness. These increase in intensity, and after three or four days the child has inflamed and swollen conjunctivæ with usually more or less lacrymation and some photophobia. The coryza is intense and there is severe bronchitis and frequently hoarseness. In some cases

these symptoms are mild and there is but little fever, while in the severest cases the child is extremely miserable and may be completely prostrated. The *eruption* is first visible in the mouth and then appears on the face about the margin of the hair and spreads as described below. The temperature may drop after the rash makes its appearance or continue for a day or two longer. The symptoms are usually most intense about the height of the rash and as it fades they lessen so that by the time the rash has disappeared the child feels comfortable. The lymph nodes over the body become enlarged, particularly the post-cervical and post-auricular, but this in some cases may be wanting. They rarely attain the size seen in rubella. The spleen is usually slightly enlarged. Heim called attention to the odor of measles which is very perceptible in a ward full of measles patients, but is too faint to be detected by the average nose in isolated cases. It is a sweetish heavy odor and has been likened to that of freshly plucked goose feathers.

Koplik Spots.—The rash had been noted in the mouth, and excellent descriptions of the spots given by Filatow, Flindt, Reubold, and Bohn, but they apparently did not appreciate their clinical significance. Koplik, in 1896, pointed out the fact that the spots which now bear his name are pathognomonic. They appear on the mucous membrane of the mouth, most frequently on the inside of the cheeks about the level of the second molar. They may also be noted on the inside of the lips and sometimes in other places. They appear as a distinct eruption which consists of small irregular spots of a bright red color and in the centre of each spot there is noted, in strong daylight, a minute bluish-white speck. Sometimes there are only a few spots, some six or a dozen, while in other cases they may cover the whole of the buccal mucous membrane. They do not coalesce but retain their punctate character. These spots are of particular value in diagnosis, as they may be seen twenty-four to forty-eight hours and sometimes three or even four days before the exanthem. These spots can be seen in fully 95 per cent. of cases, if not more, but the examination must be made by bright daylight or by a very white light, as in ordinary artificial light they are not visible. If one is familiar with their appearance there is little or no danger of their being confused with anything else. Thrush or aphthous ulcerations have been mistaken for them, but only by unskilled observers. The opening of Steno's duct should be kept in mind and also Fordyce's disease.

Enanthem.—On the first day of the fever there is a slight diffuse redness of the mucous membranes and on the second day there is considerable redness and injection of the pillars of the fauces and of the tonsils; there may be slight swelling of the tonsils. The Koplik spots may be noted at this time or during the subsequent day. On the third day the mucous membrane of the mouth is usually normal in color except for the Koplik spots and the inflammation of the fauces. About this time, or sometimes slightly before, the eruption comes out on the skin and the mucous membranes again become more or less reddened, but more in limited areas and the Koplik spots are lost in an eruption which has the same general characteristics as the eruption on the skin. This is distinct on the fourth and fifth day and usually by the sixth day or a little later there

is only a diffuse redness of the palate and cheeks; sometimes the distinct eruption persists longer. The course of the eruption in the mouth varies greatly and no set description covers all cases. The eruption occurs on all the mucous membranes and is particularly noticeable on the conjunctiva; it has been described on the larynx, the trachea, and bronchi as well as the mucous membranes of the genitalia and bladder.

Exanthem.—"The symptoms increase until the fourth day, when (although sometimes a day later) little spots just like flea bites begin to come out of the forehead and the rest of the face. They increase in size and number, group themselves in clusters and mark the face with large reddish spots of different figures" (Sydenham). The *eruption* usually appears on the third, fourth, or fifth day after the catarrhal symptoms begin, but it may come out on the first day after the beginning of the symptoms or be delayed as late as the tenth. Variations in the appearance of the rash are more frequent in young children. The rash first appears as small red spots on the temples, the forehead about the edge of the hair, and back of the ears. They are seen a little later or even at the same time scattered over the body, both back and front, and at this time there is often a mottling or marbling of the skin as if the eruption were beginning deep down. The eruption consists of minute pin-head-sized papules slightly elevated and as a rule easily felt and these are grouped sooner or later in somewhat crescentic patches about a centimeter in length. The rash spreads from one part of the body to another, the face being first affected, then the body, the arms, and lastly the legs, finally involving the palms of the hands and soles of the feet. In some places the eruption is so thickly set that it forms continuous red patches, most usually noted on the face and upper part of the chest. The extent of the eruption varies considerably, and some have but a few blotches, while others may have the entire body almost uniformly covered. The skin is really never affected in its entirety even where the rash is most marked. Normal skin may be made out by pressure or by stretching it. The earlier spots are of a rose-red color and rather bright, but later the color is that of a purple raspberry and has a characteristic tint becoming somewhat darker as time goes on until it is nearly a port-wine color or almost the shade of a purple birth-mark. After several days it fades rather quickly, leaving purplish-brown spots which in a day or two become faint yellowish-brown. This slight pigmentation persists from two or three weeks and gradually disappears.

The eruption fades in about the order it appeared and may begin to disappear from the face before it is fully developed on the feet and ankles. The small papules are sometimes surmounted by a tiny vesicle, while in others there is merely a small elevated point. Sometimes the papules are large and have a distinct shotty feel. Small *petechiæ* are common in some cases (about 5 per cent.), particularly about the wrists and ankles. They are easily produced by slightly bruising or pinching a fold of skin between the fingers. This should not be mistaken for a hemorrhagic rash. The true hemorrhagic rash is not very common, occurs in the severest form of the disease, and is spoken of as "black measles." It consists of hemorrhage into or about the great majority of the spots,

and coming on early as the eruption appears, it is nearly always the sign of a fatal issue. When it appears later the prognosis is not hopeless, although it is always grave.

There are many curious *anomalies*, and the eruption may remain incompletely developed and give the appearance of being deep in the skin; it may run an extremely rapid course or be unduly prolonged. It may fade in an irregular manner, remaining longer on the face or elsewhere than would be expected. Sometimes there is considerable itching and the skin may be broken by scratching. Sometimes ecchymotic spots may appear from the same cause. There may be free perspiration in some cases. The rash varies in appearance from many causes. It is made more intense by the patient being in a warm room or a warm bed and it is sometimes the custom to increase the amount of bed clothing to make the room unduly warm in order to "bring out the measles." If the rash is indefinite it may often be brought out by a warm bath, as is sometimes done for diagnostic purposes. Exposure to cold contracts the small arterioles and causes the rash to fade.

Circulatory failure may also cause the rash to fade. Sometimes a pemphigoid eruption is seen, usually about the fifth or sixth day, but sometimes later and with this is a rise of temperature and marked constitutional symptoms. The vesicles are large and flat often filled with thin pus and sometimes bloody serum. The patches may become gangrenous and death follow or slow recovery may take place. There may be at the same time other complications, such as pericarditis, endocarditis, pleurisy, and arthritis. Sometimes an occasional bulla is seen without the grave prognosis of the pemphigoid form. Gangrene of the skin or of the genitals may follow measles. Furunculosis, impetigo contagiosa, and ecthyma are often mentioned in connection with the rash but belong properly to complications. Occasional late eruptions are seen, and these are usually macular.

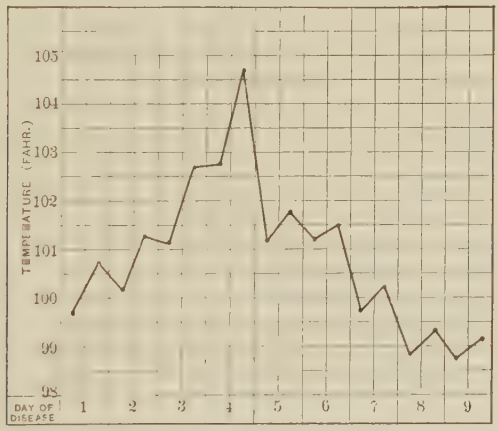
Desquamation follows in nearly every case, but may be so slight as to escape detection, and if the skin is cleansed thoroughly and oiled daily the scaling is scarcely noticeable. In ordinary conditions there are small bran-like scales which continue to come away for one or two weeks or sometimes longer. Measles without an exanthem is an anomaly which on good authority is said to be occasionally seen. Some of these cases may be explained as measles with a rash of short duration which probably happens more often than the absence of the rash.

Anomalous Cases.—These occur with considerable frequency and the disease may be light with few or no symptoms, little fever, and not much eruption. In other cases the rash may be quite pronounced with but few other symptoms or any of the more noticeable features may be absent. On the other hand, any or all of the symptoms may be very intense either at the onset or at the beginning of the eruption. There may be extreme headache with photophobia suggesting meningitis or convulsions at the onset or intense drowsiness amounting almost to coma. Epistaxis and other hemorrhages may occur especially on the third or fourth day. Catarrhal symptoms of a most intense grade may be present and the bronchitis may be so severe as to cause alarm. There may be

croupy attacks or intense hoarseness with symptoms not unlike laryngeal diphtheria. In some rare instances false membranes may form in the larynx due to streptococci or staphylococci, and the obstructive symptoms may be so severe as to require intubation. Neurotic children and those who have had whooping cough may have an intense spasmodic cough difficult to control. Occasionally there are joint pains and even arthritis with effusion.

Malignant Measles.—The disease may at times be of a particular malignant type and this may date from the onset or from the beginning of the eruption. In some instances there is hyperpyrexia and death follows with no other symptom of note. Other malignant cases are of the hemorrhagic variety in which usually at the onset of the eruption there are hemorrhages into the skin and from the mucous membranes. There may be high fever with intense prostration, and death may be caused by hemorrhage or the intensity of the toxemia. In other malignant cases there are severe symptoms, such as headache, vomiting, diarrhœa, high fever, a weak, rapid pulse, hemorrhage, and intense nervous features, convulsions or coma, and death.

FIG. 20

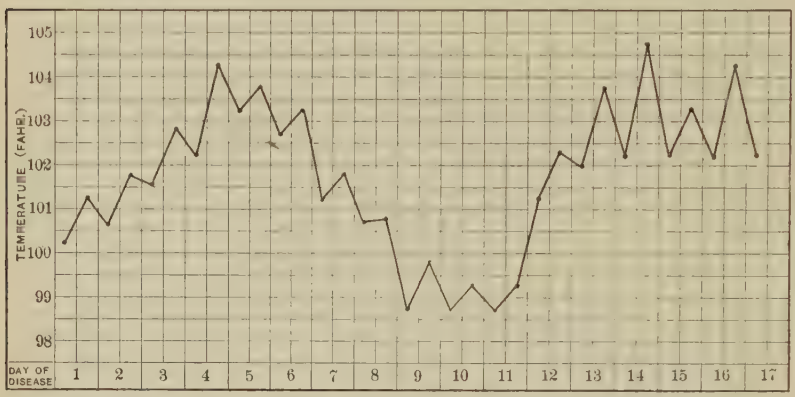


Measles temperature chart, showing sudden fall at the appearance of the eruption. Personal observation.

Temperature.—As a rule there is no fever during the incubation period, but with the onset of the catarrhal symptoms the temperature begins to rise and reaches 100° or 101° F. in the evening. The following morning it falls as a rule, although it may remain the same or even go higher. The temperature rises every evening to remit slowly on the following morning until the third or fourth day when 104° or 105° F. is reached. With the appearance of the rash, the temperature falls slowly during the next few days and is lower each morning with a slight increase in the evening until normal is reached. This seems to be the most general course in uncomplicated cases. Not infrequently at the beginning of the symptoms there is a sharp rise to 103° or 104° F. and after several

hours a fall to normal and later the regular rise begins. In exceptional cases the temperature may rise suddenly at the invasion and remain high with slight morning remission until the eruption appears. Another com-

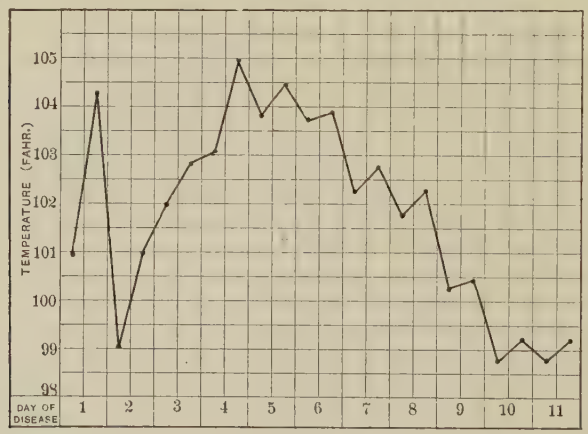
FIG. 21



Measles temperature chart, showing a complicating pneumonia coming on after the temperature had fallen to normal. Such a temperature can always mean a complication.

mon occurrence is a sudden drop in temperature with the appearance of the rash. In some there is no subsequent rise of any importance. In others the temperature may rise to 102° or 103° F. and then fall during the next two or three days. Any sudden rise in temperature a day or two after the eruption is out may be regarded as an indication of some

FIG. 22



Measles temperature chart, showing initial rise and fall. Personal observation.

complication, and if the temperature remains as high as it was for more than a day or two after the eruption has made its appearance, it indicates the same thing. In such cases the respiratory tract, particularly the

lungs, should be examined with special care. Otitis media is another cause of high temperature.

Blood.—There is a leukocytosis beginning during the period of incubation, reaching its maximum during this period and lasting into the first part of the stage of invasion. During the latter part of the stage of invasion or the beginning of the eruptive stage, the leukocytes fall to normal and there may be leukopenia. During this stage a leukocytosis means some complication, although complications may exist without it. The polynuclear neutrophiles are increased during incubation, invasion, and eruption, fall below normal with defervescence, and reach normal in convalescence. The lymphocytes are decreased at first but increased later. The large mononuclears and transitionals are normal at first but are also increased in the later stages, while the eosinophiles are decreased during the eruption but increase later. The myelocytes are present in small numbers during the eruption. The normal leukocyte count is generally reached during the fifth day of the eruption. It should be remembered that the blood findings may be so altered by complications as to be of little value in diagnosis or prognosis.

Urine.—Albuminuria is usually present during the febrile period but nephritis is rare. The diazo reaction is found in about 80 per cent.

Complications.—These are frequent and important, and it may be difficult to draw the line between symptoms and complications. More or less marked complications occur in over two-thirds of the cases.

Eye.—Injection of the conjunctiva and usually a distinct conjunctivitis with a certain amount of photophobia and often blepharospasm always occur. If the child is kept in a darkened room and some mild antiseptic eye-wash applied frequently there is generally no further trouble. Sometimes there is inflammation of the cornea or the inflammation may extend to the lacrymal glands or there may be blepharitis. Sometimes weakness of accommodation may follow measles and occasionally there may be paralysis or spasm of the ocular muscles. Amblyopia is rare and has been followed by optic atrophy.

Ear.—Acute catarrh of the middle ear is not infrequent and may cause headache, slight deafness, or tinnitus. Occasionally the inflammation becomes purulent and sometimes there is mastoiditis.

Gastro-intestinal.—Stomatitis is present in every case, usually only catarrhal, but ulcerative stomatitis may prove serious. Gangrenous stomatitis is occasionally seen; the destruction of tissue is painless and rapid and there is a characteristic fetid odor. Vomiting is not more common than in other febrile diseases, and while acute gastritis may occur, disease of the intestine is more frequent, diarrhœa often being present; ileocolitis may be a major complication. In the severest form the colon and lower part of the small intestine are affected.

Respiratory Tract.—This is frequently involved and nearly every patient has coryza which may be purulent. The larynx is frequently inflamed with hoarseness, croupy cough, and sometimes loss of voice and symptoms of obstruction. These cases may be difficult to differentiate from laryngeal diphtheria. Severe laryngeal inflammation is always dangerous, and membranous laryngitis is second to pneumonia

as a cause of death in measles. Sometimes persistent hoarseness follows the disease.

Tracheitis, tracheo-bronchitis, and bronchitis are all frequent. The bronchitis may extend into the smaller tubes and bronchopneumonia follow. In the severer forms of this there is marked cough, dyspnœa, and cyanosis, the pulse becomes rapid and weak and death may ensue. The physical signs are the sinking in of the ribs during respiration and numerous fine rales heard all over the chest, while coarse rales are not uncommon. Areas of dulness cannot be made out. The breathing is shallow, the diaphragm in consequence is high, and the liver dulness may be mistaken for consolidated lung.

Bronchopneumonia is the most frequent of the more serious complications and is responsible for more deaths than any other cause. Henoch states that some pneumonia is found in every fatal case. The symptoms, course, and physical signs do not differ from ordinary bronchopneumonia, but in measles the temperature cannot be relied on to differentiate pneumonia and bronchitis. If there are symptoms of bronchopneumonia, even though not marked, it is safe to assume that it is present. Pneumonia may be suspected if the temperature is above the average or if the child is apathetic with rapid and irregular respiration. There is no regular course for this pneumonia as it may last a week with irregular fever or persist for six weeks, the fever running now high, now low, sometimes subnormal, and sometimes above 105° F. The process may stop and go on to recovery at any time. Following bronchopneumonia, especially a persistent attack, there may be bronchiectasis, and fibrosis is not an infrequent sequel. Bronchopneumonia is frequent in asylums and hospitals and among the poor, and occurs more often in weak than in robust children. It is more common in overcrowded wards. Lobar pneumonia is sometimes seen, and there are cases which may be regarded as abortive pneumonia. The temperature is high for a day or two, the child is prostrated, somewhat cyanosed, and the respiration rapid, but after one or two days the symptoms and signs disappear. Empyema should always be borne in mind where there have been lung complications, and gangrene of the lung may follow. In some epidemics pleurisy is frequently noted.

Circulation.—Involvement of the heart is not common unless other complications are present. Pericarditis is sometimes seen, but more frequently escapes notice until the autopsy. Endocarditis and myocarditis are probably due to the complication which caused death.

Nervous System.—Convulsions are occasionally seen at the onset, and headache, backache, and neuralgia are not infrequent. Contractures of the muscles sometimes occur early and during convalescence. Various forms of paralysis, hemiplegia, paraplegia, due to myelitis and general neuritis, have all been reported, but are rare. Temporary insanity, chorea, and epilepsy have all been ascribed to measles.

Skin.—Urticaria, furunculosis, impetigo contagiosa, and ecthyma are the most frequent complications. Erythema nodosum and erysipelas have been reported. Pemphigus is frequent; it may be very extensive and accompanied by severe constitutional symptoms and sometimes

gangrene of the skin and death. Gangrene of the skin may occur alone but is usually an extension of gangrene extending about the cheek or vulva. Measles is reported as sometimes having a curative effect upon eczema, particularly upon the facial type.

Bones and Joints.—Arthritis may occasionally be seen, the knee being most frequently affected, and osteomyelitis has also been noted.

Pregnancy and Measles.—Cerf has studied the effect of measles in pregnancy, and his figures show that it causes abortion in 60 per cent. of the cases. The more advanced the pregnancy the more probable is the abortion, and after the seventh month there is premature birth in 80 per cent. There were no postpartum complications in these cases.

Measles and Other Infections.—When measles and chicken-pox are seen together they both run their accustomed course. If the chicken-pox appears first the diagnosis is easy. After the measles rash appears the diagnosis may present great difficulty. Smallpox and measles together may produce a difficult clinical problem. The measles exanthem may be distinguished between the pocks, but if the smallpox is confluent the measles eruption may be indistinguishable on the face. An attack of measles undoubtedly lowers the resistance, and any infection may be seen as a complication. Tuberculosis may be regarded as a complication or sequel of measles.

Diagnosis.—This is usually easy after the rash has appeared, although at times it may test the ability of the clinician to decide upon the nature of a morbilliform rash and cases without eruption are almost always doubtful. To be of the greatest preventive value, the diagnosis should be made in the preëruptive stage. The early leukocytosis is of value if a blood-count can be made. If measles is suspected, drowsiness, cough, coryza, and conjunctivitis are sufficient to make a tentative diagnosis. The Koplik spots are of special value, and the most frequent cause of failure to find them is a lack of knowledge of their appearance, the use of poor or artificial light, and a hurried examination. Meunier has called attention to a loss in weight by the fifth or sixth day of the incubation period.

Scarlet fever is distinguished by the sudden onset with vomiting, high fever, the characteristic rash, the angina, and the strawberry tongue. *Rubella* is easily confused, but in epidemics the absence of catarrhal and other symptoms, the absence of Koplik spots, and the presence of the characteristic enanthem and especially the polymorphous character of the exanthem make the diagnosis easy. *Smallpox* is the most important disease with which measles may be confused. Despite the apparent difference, the two diseases may be strikingly similar, especially about the beginning of the rash. Measles is perhaps more often mistaken for smallpox than the reverse. In smallpox there is usually an initial chill, vomiting, backache, and fever, and when the eruption appears the fever falls and the patient feels comparatively well. In some cases of measles there may be severe symptoms at the onset and with the appearance of the eruption the temperature may fall, although this is not the rule. If the measles rash happens to have a distinctly shotty feel the clinical picture may be almost, although not exactly, the counterpart of smallpox.

The measles exanthem is finer, much more abundant and more in patches than the eruption of smallpox as seen in the mouth. On the first day or two of smallpox there are small red papules seen best on the palate. If Koplik spots are present they are of great aid, but they may be obliterated before the patient is seen. The exanthem of measles is frequently on the face, chest, and back, while smallpox is not confluent as a rule on the trunk, but frequently so on the face, forearms, and wrists. The measles eruption is arranged in crescentic patches while the smallpox eruption is not. The history of exposure to one disease or the other is of some value, but if doubt exists it is better to isolate the patient and wait for twenty-four hours, when the diagnosis is usually clear. The prodromal rashes in smallpox may be morbilliform and have been mistaken for measles, but the absence of Koplik spots and catarrhal symptoms render it plain that the rash is not measles whatever else it may be. *Typhus fever* has the same catarrhal symptoms but as a rule the general symptoms are more intense. The onset is more sudden and the eruption becomes hemorrhagic after the first, second, or third days and consists rather of spots and blotches. *Influenza* may be mistaken for measles at the onset and also a septic infection with an eruption. The absence of catarrhal symptoms and of Koplik spots is of considerable value. *Syphilitic rashes* may occasionally be morbilliform, and if there is fever at the same time may be mistaken for measles. The presence of other manifestations and the longer duration of the rash are the most distinguishing features. The enanthem in these cases is of particular diagnostic value. *Serum rashes* are usually scarlatiniform or urticarial but may occasionally resemble measles. They may be distinghished by the absence of the characteristic enanthem and prodromes. *Drug rashes* are extremely liable to be confused with measles. The history of taking the drug, the absence of symptoms and of fever usually render the diagnosis plain. Antipyrine produces a measles-like eruption. The arrangement is less crescentic than in measles, and unlike measles, it does not spread after it once appears. Quinine rashes at times may resemble measles and may even spread from above downward. Copaiba, cubebs and other balsams, ethereal oils, turpentine, chloral, and others, may cause a measles-like eruption. In one instance the writer saw the rose spots in typhoid fever so numerous as to suggest measles but there was no crescentic arrangement and no other symptoms suggestive of measles.

Prognosis.—This must be guarded in any given case. Measles is usually regarded by the laity as a mild disease but a very large number of deaths are caused by it. The mortality varies in different epidemics between 3 and 50 or more per cent. It varies greatly with the age and surroundings. In private practice among the better class measles is not a dangerous disease, but among the poorer classes and in hospitals and asylums it may prove a veritable scourge. Age is an important factor, and from birth to six months of age there are few deaths owing to the comparatively few cases. From six months to two years of age there is a steadily increasing death-rate which then declines until about the fifth year, after which deaths from measles are comparatively infrequent. The sexes are affected about equally. After forty the mortality

increases with the age and in old age it is extremely fatal. There are more deaths in winter weather than in summer, partly owing to the greater number of infections but largely due to the greater number of pneumonia cases. Death is nearly always due to complications, the most frequent fatal ones being bronchopneumonia, bronchitis, laryngeal affections, diarrhœa, ileocolitis, tuberculosis, and noma.

Prophylaxis.—Nearly everyone has had measles at some time, and many of the laity take no pains to guard their children from infection. As the mortality decreases after two years of age and is comparatively slight after five years, every effort should be made to put off infection until after the fifth year. Quarantine is without doubt the best means for preventing the spread of measles. Susceptible children and all visitors should be prevented from entering houses where there are cases of measles and when this cannot be done the patient should be removed if possible to an isolation hospital. School inspections have done much to lessen measles and children under suspicion should not be allowed to attend. Any child with suffused eyes, cough, and sore throat should be sent home to await developments. During severe epidemics, schools should be closed and children's parties be prohibited.

Prophylactic Injections.—Blood serum from patients convalescing from measles confers a temporary immunity. It should be preserved with 0.2 per cent. trikresol. It is given in 5 cc. doses, intramuscularly and is most useful up to six days after exposure; later the results are not so good and after eight days the results are very uncertain. If it does not prevent, it lessens the severity of the attack. This method is useful in preventing epidemics in hospitals and institutions.

Herman, depending upon the fact that infants up to five months of age share the maternal immunity to measles, inoculated such infants with the virus contained in the nasal discharge from measles patients. The subjects developed a slight reaction and were apparently rendered immune. This work, done in 1915, seems to have received little attention. Some such method of active immunization in infants is greatly to be desired, since the highest mortality is in the first three years of life.

Isolation.—In hospitals and institutions for children every suspicious patient should be isolated. Large hospitals for children should have a quarantine ward in which children who have not had measles can be isolated until two weeks have passed, as epidemics in hospitals are usually started by the admission of a child in the incubation period. The isolation room or ward should be in a detached building. Where this is not practicable the room should be as far removed as possible and be strictly quarantined from the remainder of the building. Isolation in small hospitals and in private houses unless carried out in this manner is liable to prove futile. Isolation in a small room off the end of a ward may do better than no isolation at all, but certainly where children are concerned it is not very useful. The difficulty in isolation consists of the fact that it can rarely be done sufficiently early. The disease may be transmitted before its presence is suspected, and the children with whom the patient has come in contact are infected before the disease has been diagnosed. This is particularly true in private families where the

question of isolation is an open one, but if the susceptible children can be sent away as soon as the disease is discovered that is the best thing to do. Such children should not be sent to homes where there are other susceptible children as the children so sent are frequently infected. Isolation in the average household is usually not strict enough to be of service or is started too late. After measles it is well to give the apartments a thorough cleaning and have them well aired for several days. Disinfection is unnecessary.

Treatment.—The child should be placed in a convenient room, and plenty of fresh air is desirable; but ventilation should be accomplished without strong drafts. The temperature should be about 70° F., and kept as equable as possible. There is no advantage in superheated rooms, an idea very prevalent among the laity. If there is photophobia the room should be sufficiently darkened to be comfortable.

It is well to have the skin anointed with some bland ointment, and equal parts of vaseline and lanoline are satisfactory. The skin is kept clean by sponging with warm water and castile soap twice daily, after which the ointment is applied. If there be itching, sponging with warm carbolic acid solution (1 per cent.) is useful, or carbolated vaseline or a coarse talcum powder may be applied. There is a rooted objection in most families to using water on measles patients, and when this cannot be overcome or when the child is liable to be chilled by exposure, all attempts at sponging are best abandoned.

The *diet* should be the same as for any acute fever. Bottle-fed infants should have their food diluted, and older children should be placed upon liquid diet. Food should be given at regular intervals, two, three or four hours apart, depending on the amount given at one time. Plain or carbonated water, lemonade, orangeade, grape juice, and water, and similar drinks may be used to allay thirst. After the subsidence of the fever a gradual return to solid food should be made. If gastro-intestinal disorders appear, the usual rules of diet for these should be observed.

Fever.—Moderate fever may be disregarded but if the temperature is very high or accompanied with great nervousness it may be reduced by sponging with equal parts of alcohol and tepid water. An ice-bag to the head is grateful if there is headache. In giving baths to measles patients care should be taken to avoid exposure. If the feet become blue and cold, warmth and friction may be applied to them. If the temperature is high and the child feels cold to the touch a warm bath is indicated. Antipyrine is useful in patients with a good strong heart, but need not be given for the fever alone. It is useful in combating nervousness and cough.

Nervousness and Sleeplessness.—These are frequently allayed by bathing or sponging. If these do not suffice, codeine and antipyrine may be given. A child of one year may be given $\frac{1}{24}$ of a grain of codeine sulphate with 1 grain of antipyrine in syrup of orange. This may be repeated, and will be found useful for controlling irritability and cough. Phenacetine may be given for the same purpose.

Eyes.—The conjunctivitis requires a mild antiseptic eye-wash. Ten grains of boric acid with 1 dram of camphor water and 7 drams of distilled water is suitable. If the lids are adherent in the morning, the edges should be anointed at night and once or twice daily with a salve containing 1 grain of yellow oxide of mercury to 4 drams of vaseline.

Nose, Throat, and Mouth.—These should be kept clean by douches, sprays, or gargles. As a rule the nose is best kept clean with a nasal douche which flushes without pressure, thus avoiding the possibility of forcing the secretions up the Eustachian tube. Dobell's solution is satisfactory. The throat is usually best cleansed by using Dobell's solution in an atomizer, but older children may use a gargle. The mouth should be kept clean by a spray or by absorbent cotton wrapped about the finger, and moistened with boric acid solution, Dobell's solution, or diluted peroxide of hydrogen.

Laryngeal complications are best treated by inhalations, such as creosote, oil of eucalyptus, or compound tincture of benzoin. A dram (4 cc.) to a pint (500 cc.) of water may be used. This is also useful in bronchitis and bronchopneumonia. External applications—heat, cold, or counterirritants—may be made over the larynx.

Bronchitis.—Inhalations as advised for laryngeal complications will be found useful. Antipyrine and codeine will be found of service. Heroin hydrochloride may be used if the cough is very irritable. Small doses of syrup of ipecac and sodium bromide given in syrup of orange are also useful.

Bronchopneumonia.—This is treated as under ordinary circumstances; inhalations, counterirritation, and stimulants, as indicated, are the best forms of medication. The chest should neither be weighed down with plasters nor poultices, nor should heavy jackets and innumerable undershirts be used. The chest should be allowed full freedom and the air of the room should be kept fresh, and gas stoves and unnecessary attendants excluded.

Gastro-intestinal Complications.—Vomiting is best treated by withholding all food. If this does not avail and if the patient is under a year of age or sufficiently tractable the stomach may be washed out. A useful prescription is equal parts of cinnamon water and lime-water, of which a teaspoonful may be given fifteen minutes before feeding, and repeated several times if necessary. Effervescing drafts are also useful. Diarrhœa and ileocolitis are best managed by clearing the intestinal tract and careful dieting. Bismuth subcarbonate is most useful.

RUBELLA

Definition.—Rubella is a specific infectious disease occurring in epidemics, characterized by a polymorphous rash which sometimes resembles that of measles, sometimes that of scarlet fever, and sometimes that of both diseases; by little or no constitutional disturbance, and by almost constant enlargement of the cervical and sometimes other lymph nodes.

Etiology.—Rubella exists as a separate disease, and an attack does not protect against either scarlet fever or measles, nor does an attack of

either scarlet fever or measles protect against rubella. It occurs in epidemics and is rarely seen sporadically. The sporadic cases are usually part of small family or school epidemics.

Rubella may be transmitted by direct contact and by fomites, especially clothing or bedding, but the contagious principle has not yet been discovered. The infectiousness seems to vary in different epidemics. In a small epidemic observed by the writer there were 14 cases in a ward containing 22, or 63.6 per cent. The disease was not carried to any other part of the building, although the maids and nurses went about freely and the clothes were sent to the laundry without sterilization. The children with rubella were up and went through the same halls as the other children, but used a separate play-room and were not allowed to come in contact with the children from other dormitories. In this epidemic it appeared as a disease transmitted by direct contact and not by fomites or a third person. The disease is infectious early, perhaps before the eruption appears, and this lasts as long as the eruption. Comby states that the infectiousness disappears with the eruption.

Sex and Age.—The sexes are affected equally. Scholl reported a case in which the pregnant mother (seven months) transmitted the disease to the unborn child, the disease making its appearance several days after birth. Young infants are as a rule immune. It is most frequent in early childhood, while older children and adults are less frequently affected. Hatfield states that the liability varies inversely with the age, whilst Ashby regards adults as even more liable if exposed.

Station in Life.—The disease is more frequent among the poor than the well-to-do, which may be explained by the lessened resistance and the greater danger of exposure.

Immunity.—One attack generally protects and second attacks are very rare.

Incubation Period.—This is ordinarily stated as being from fourteen to twenty-one days. The shortest period is one day (Griffith and Atkinson) and the longest four weeks (Klaatsch).

Symptoms.—Prodromes.—There may be none at all, the rash being the first thing noted; or there may be some indisposition from several hours to two days, and exceptionally as long as four days, before the rash appears. The most common prodromes are headache, backache, loss of appetite, nausea, and sometimes vomiting, slight fever, drowsiness, and, in some, agitation. Convulsions have been reported at the onset and occasional symptoms are redness of the eyes, a little dysphagia, some hoarseness, and occasionally sneezing.

Invasion.—This may be slight or severe. In some the only thing noted is the appearance of the rash, or there may be chilliness, languor, headache, with pain in the back and extremities. There may be more rarely coryza, congestion of the conjunctivæ, slight pharyngitis, hoarseness, cough, nausea, and vomiting. There may be epistaxis, and Priolean reported an initial hemorrhage from the eyes and ears. Urticaria and other rashes may precede the initial eruption. The stage of invasion may last from several hours to five days; these symptoms show great variations and may disappear before the eruption.

Temperature.—This varies greatly in different epidemics. There may be no fever or it may in rare instances reach as high as 104.3° F. When the temperature is high it remains so but a short time. In the average case the fever is slight and lasts from two to four days, ranging from 100° to 102.5° F., with slight evening exacerbations. The highest temperature is seen usually at the beginning of the eruption, and to a certain degree corresponds to it, the most marked rashes being attended with the highest fever. The exacerbations which follow never reach as high a point unless there is a relapse or some complication.

Eruption.—The most characteristic feature is the polymorphism, and in one patient it may resemble scarlet fever rather closely; in the next it may be like measles, while in a third it may on one part of the body resemble scarlet fever and on another measles. It may be accompanied by itching or burning, while at other times there are no abnormal sensations. In the majority it affects the face and scalp first, then the neck and body, spreading from above downward, involving the arms, and lastly the legs and feet. It may spread irregularly and on certain parts of the body be more intense than on others. When more or less continuous pressure is made on the skin, as about the waist or neck band, or on the back or side when the child is in bed, the eruption is more marked. There are patches about the lips in most instances. The eruption may be seen on the palms and soles. In the writer's experience the morbilliform rash is more frequent, and it may be that alone or mixed with other varieties. It is not uncommon to have a measles-like rash over the face and most of the body, while over the parts pressed upon, the buttocks and the inner sides of the thighs, it is scarlatiniform. The rash frequently can be seen in the deeper layers, bluish-red macules rather crescentic in shape mottling the skin like marble. Later these appear as rose-red spots, made up of numerous small pin-head-sized papules, slightly raised above the surface, and to the touch like shot under the skin. In some the patches are discrete and in others they may run together. The early rash may suggest flea or other insect bites. In still other cases the little pin-head-sized papules may be nearly all discrete. The rash fades rather quickly and may be fading on one part of the body while spreading on another. The eruption reaches the greatest intensity usually on the second day and then begins to fade, the entire process lasting from one to two days to a week. The duration of the rash is extremely variable, and it may last but an hour or two or as long as fifteen days. The average duration has been stated as from one to six days, three to four days, and four to five days. The variation in the duration of the eruption is one of the distinctive features. Cases without any eruption have been reported.

Following the fading of the rash there may be a light brownish-yellow discoloration, which disappears in from one to three weeks. There may be the separation of fine bran-like scales for several days or no apparent desquamation. Purpuric spots, vesicles and petechiæ over the entire body have been mentioned.

Eruption in the Mouth.—Forcheimer called attention to the eruption in the mouth, and this in the writer's experience is a constant feature,

being noted at the time of the appearance of the rash on the body. Forcheimer described it as follows: "It consisted of a macular, distinctly rose-red eruption, upon the velum of the palate and the uvula, extending to, but not on, the hard palate. The spots were arranged irregularly, not crescentically, of the size of large pin-heads, very little elevated above the level of the mucous membrane, and did not seem to produce any reaction upon it." This eruption lasts for twenty-four hours or less, but in some cases can be seen on two successive days. This eruption in the mouth is unlike that seen in measles and also differs from the scarlet fever angina.

Blood.—There is a leukocytosis (polynuclear) during incubation, followed by leukopenia when the eruption appears. After the disappearance of the eruption the blood becomes normal.

Lymph Node Enlargement.—This is a marked feature; there is a striking enlargement of the posterior cervical lymph nodes in nearly all cases. It may also affect the submaxillary, post-auricular, and suboccipital nodes. The size varies; they may be small or as large as a pigeon's egg. The enlargement comes on about the same time as the rash, but may precede it by several days. The swelling gradually subsides with or after the disappearance of the rash. The nodes do not suppurate.

Malignant Rubella.—Edwards and others have reported fatal cases with vomiting, convulsions, delirium, and high fever. The temperature was high (104° F.) and the heart weak and rapid. The pulse-rate in some cases was 150 or over and in some there was heart failure. Pneumonia and diarrhœa were the most common complications.

Complications.—These are rare, but occasionally one or more of the following may be observed: pneumonia, pleurisy, bronchitis, croup, earache or otitis, arthritis, erysipelas, stomatitis, temporary enlargement of the thyroid, convulsions, or delirium. Complications are so rare that they may almost be regarded as coincidences.

Relapses and Recurrences.—Recurrences are very rare as the immunity is apparently lasting. Relapses are rare but do occur.

Diagnosis.—The polymorphous rash, the eruption on the uvula and soft palate, and the glandular enlargement with an absence of other symptoms, are the most important features. Rubella occurs in epidemics, and sporadic cases are to be looked on rather as measles or scarlet fever. It must be distinguished from drug rashes, especially that from copaiba. The so-called roseola simplex due to heat or indigestion and so common in infancy must not be confounded with it. Dukes called attention to a rash caused by handling certain varieties of caterpillars, which might be mistaken for rubella. Comby gives the absence of the diazo reaction as one of the signs in differentiating scarlet fever, and the absence of Koplik spots and catarrhal symptoms is of especial value in excluding measles.

Prognosis.—This is almost invariably good. Fatalities are so exceptional as to be regarded as due to the accidental association of some other disease. Epidemics have been reported with a considerable mortality, as one by Edwards in which it was 4.5 per cent.

Treatment.—This is very simple. If the child has fever he should be kept in bed; but if there is no fever and the child feels well there is no danger in allowing him to be about. Small doses of spirits of nitrous ether may be given if there is fever, and phenacetine, with small doses of codeine, if there is much restlessness and nervousness. As a rule no treatment whatever is required.

THE FOURTH DISEASE

In 1900, Clement Dukes, physician to the Rugby School, described an infectious disease which he called "The Fourth Disease." This affection has been discussed by numerous observers. The incubation period was about the same as that of German measles, nine to twenty-one days. Prodromes were usually absent, but malaise and some sore throat were sometimes present at the onset of the rash. The rash appeared rapidly and covered the body in a few hours. Dukes does not mention whether it appeared on the face or not. The color of the rash was said to have been brighter than that of scarlet fever and was followed sometimes by slight and sometimes by marked desquamation. There was some glandular enlargement. The temperature was usually not over 101°, but in one instance it was 104° F. There were no sequelæ and the attack did not protect the individual against scarlet fever or rubella.

ERYTHEMA INFECTIOSUM

Definition.—Erythema infectiosum is a feebly contagious disease of childhood characterized by a maculo-papular, rose-red rash, especially marked on the face and the external surfaces of the extremities, and by slight or no subjective symptoms.

Etiology. The exciting cause is unknown. The disease usually occurs in epidemics, most frequently in spring and summer, and children between the ages of four and twelve years are most often affected. Close contact is required to communicate the disease. An attack does not protect from measles, scarlet fever, or German measles.

Pathology.—No autopsies have been reported, and the only lesions known are erythema and occasionally slight pharyngitis.

Symptoms.—The incubation period has been from six to fourteen days in the cases in which accurate observations could be made. There may be slight prodromes, as malaise and sore throat, but usually the appearance of the eruption is the first sign of the disease. On the first day the rash appears on the face and is described as a rose-red efflorescence which covers the cheeks, extending to the naso-labial folds in front, to the temples above, and laterally as far as the angles of the jaw. Over this area the rash in confluent, slightly raised above the surface, and for the most part sharply outlined, although in places it may fade gradually into the healthy skin. The general appearance is that of erysipelas, but while the skin is hot to the touch it is not sensitive and does not itch. There is no subcutaneous hemorrhage on pinching the skin. The rash disappears on pressure but reappears quickly when the

DIFFERENTIAL DIAGNOSIS OF RUBELLA, SCARLET FEVER, MEASLES AND ERYTHEMA INFECTIOSUM.

	RUBELLA.	MEASLES.	SCARLET FEVER.	ERYTHEMA INFECTIOSUM.
CONTAGION	Apparently varies in epidemics. Direct contact. Possibly from fomites, not through the air.	Highly contagious. By direct contact. By fomites. Through the air.	Marked. By direct contact. By fomites.	Feeble. Usually by direct contact.
INCUBATION.	Variable average 1 to 3 weeks.	Average 9 to 14 days.	Average 1 to 6 days.	Average 6 to 14 days.
PRODROMES.	Slight and of short duration. Occasionally a day or two of malaise.	3 to 4 days. Drowsiness and catarrhal symptoms.	Short or wanting —onset usually sudden.	Very slight and of short duration.
KOPLIK SPOTS.	None.	Present in 90 or 95 % of cases.	None.	None.
VOMITING.	Rare.	Occasional.	Common.	Uncommon.
FEVER.	Slight—average 1 to 2 days, sometimes for 4 days, seldom more than 101 to 102 degrees.	Marked high curve lasting about a week, average from 102 to 104 degrees.	High fever lasting about a week, averages 104 to 105 degrees.	Little or none.
CATARRHAL SYMPTOMS.	Slight.	Marked.	Absent.	None.
TONGUE.	Slight coat, nothing characteristic.	Tongue coated, that of any fever.	Strawberry, later mulberry tongue.	Sometimes slightly coated.
THROAT.	Small punctiform red spots over uvula and palate. Pharynx slightly reddened.	Moderate pharyngitis and redness of mucous membranes.	Usually a severe angina.	Sometimes very slight sorethroat at onset
DIARRHŒA.		Frequent.		
LYMPH NODES.	General enlargement, especially of post cervical nodes.	Postcervical, postauricular, and submaxillary nodes enlarged.	Depends on extent of throat involvement, glands at angle of the jaw involved.	Not enlarged.
PULSE.	Varies with fever.	Varies with fever.	Very rapid.	Normal.
ALBUMINURIA.	Rare and slight.	Rare.	Common.	None.
ERUPTION.	Begins on face, spreads to neck and breast then to arms, legs and feet. Is fading from older parts while spreading to new. Two forms—common form, morbilliform, small, slightly elevated papules, discrete, sometimes confluent, more rarely scarlatiniform, lasts 2 to 4 days or less, color rose-red but this varies.	Begins on face, spreads gradually over entire body. Covering it by the second or third day, consists of small papules arranged in crescentic groups, these are confluent in places, lasts 4 to 5 days. Is deep red, often purplish.	Begins on neck and chest spreads slowly over entire body —maximum about the fourth day. Does not affect lips. Consists of small punctate spots or a diffuse blush, disappears on pressure, lasts about a week. Intense red color.	First on face as symmetrical, rose-red blush, for the most part sharply defined and resembles erysipelas. It is hot to the touch but not sensitive and it does not itch. The second day it spreads to the body and extremities, small discrete crescentic patches over the body and sparingly on the inner and flexor surfaces of limbs. Marked map-like eruption on outer and extensor surfaces. Begins to fade on face in 4 or 5 days. Lasts altogether 6 to 10 days.
DESQUAMATION.	Slight and branny.	Branny.	Marked in flakes and large pieces.	None.
CONVALESCENCE.	Rapid, no complications.	Slow, frequent complications as pneumonia. Later other infectious diseases as tuberculosis.	Slow, complications frequent as nephritis, otitis media, etc.	Rapid, no complications.

pressure is removed. On the following day the eruption extends to other parts of the body and on the forehead and chin there are discrete patches. It spreads slowly downward, and on the trunk there are discrete somewhat crescentic patches, from an eighth to half an inch long and suggesting measles, which may also at times be wheal-like, resembling urticaria. The eruption is marked on the extensor and outer surfaces of the arms and legs, and about the elbows and buttocks it may be confluent. Over the extremities the rash is morbilliform and the spots run together, forming map-like areas, which are especially marked when the eruption begins to fade. Shaw suggests that it resembles lace work. The color varies from a rose-red to a brownish-red. The hands and feet are the last places to be affected, and the mucous membranes are not involved. The eruption fades first from the face after four or five days, and a few days later disappears from the body. In all it lasts from six to ten days, and in some cases may disappear and then reappear after a short time. There is no subsequent pigmentation or desquamation.

There are practically no subjective symptoms, although there may be a slight sore throat at the onset and the tongue may be somewhat coated. There is no glandualr enlargement.

Diagnosis.—This depends largely upon the recognition of the rash, and is not difficult. The following are the most striking points of difference: *Scarlet fever*—Marked constitutional symptoms, high fever, strawberry tongue, angina, and a uniform rash. *Measles*—Marked constitutional symptoms, fever, catarrhal symptoms, and Koplik spots. *Rubella*—Enlarged lymph nodes, especially the posterior cervical, and the presence of the eruption over the soft palate and the uvula. *Drug Rashes*—The history of taking drugs. *Urticaria*—The itching. *Erythema exudativum multiforme*—This begins on the hands and feet, becomes vesicular, lasts for weeks, and is attended by marked constitutional symptoms. Erythema infectiosum is not to be confused with the so-called "fourth disease," in which there is said to be a scarlatiniform rash making its appearance in a few hours and often followed by desquamation.

Prognosis.—This is favorable, as there have been no fatal cases reported, and there are neither complications nor sequelæ.

Treatment.—There are no indications for treatment.

MUMPS

Definition.—Mumps is a specific infectious disease characterized by fever and by swelling and tenderness of the salivary glands, usually the parotids, but sometimes the submaxillary and sublingual glands. Metastases occasionally occur in other organs.

Etiology.—Mumps occurs in epidemics, especially in schools and barracks, and is endemic in the larger cities. Epidemics are apparently uninfluenced by weather or climate, and the sexes are about equally affected. The majority of the cases occur in children between five and fifteen years of age. Under five years the susceptibility to the disease is not great, and after fifteen it diminishes with age. Nursing infants are usually immune and may not contract the disease even when nursing

the breast of a woman with mumps; but cases have been reported during the nursing period. The disease may be transmitted through the placental circulation. White relates a case of a woman whose child showed signs of the disease six days after delivery, and the mother had swelling of the parotid on the following day. Individuals of sixty or seventy years are not immune.

Epidemics in institutions are usually slow and last several months, new cases developing from time to time; from one-quarter to one-third of those exposed take the disease. They are often confined to one set of buildings or to one enclosure.

The disease is transmissible evidently before the symptoms appear, and for some time, even as long as six weeks, after they have disappeared. Transmission is usually by direct contact, and the disease is not transmitted through the air and only rarely by a third person or by fomites. Roth relates a case contracted by sleeping in a bed previously occupied by a patient with mumps, and instances are on record of a nurse infecting other persons.

Incubation Period.—This is usually long and variously stated. Roth placed the average at eighteen days, with a minimum of four days and a maximum of twenty-five days, while the commission of the Clinical Society of London set the incubation from fourteen to twenty-five days. However, the average period is nearer three weeks than two. There are undoubted cases in which the disease has developed after thirty-five days, and even after six weeks.

Immunity.—One attack generally confers immunity; but second attacks are by no means rare, and third attacks have been reported.

Bacteriology.—A number of organisms have been described. Wollstein injected a bacterially sterile filtrate of the salivary secretion of children and adults suffering with mumps into the parotids and testes of cats; after five to eight days there were rise in temperature, leukocytosis and changes in the inoculated organs.

Pathology.—There is intense hyperemia and œdema of the gland, with considerable infiltration around it. There are no subsequent changes in the gland.

Symptoms.—Prodromes may or may not be present. They are usually noted in about one-third of the cases, and come on from twelve hours to two days before the swelling appears; but in some cases there may be prodromes from four to even eight days. The usual prodromes are fever with or without a chill, general malaise, vertigo, drowsiness, vomiting or diarrhœa, and epistaxis, and there may also be sweats, fainting spells, pain in the ear, and trismus. The *symptoms* proper are principally the glandular swelling, pain, and fever. The parotids are usually affected, and one or both sides may be involved. The gland enlarges rather rapidly for from three to six days, then remains stationary for a day or two, and gradually subsides. The subsidence is usually complete in a week or ten days, although in severe cases it may be three weeks or a month before the enlargement has disappeared entirely. The left side is more frequently affected than the right, and where both sides are not affected at the onset the opposite side is generally involved in from one to four

days. In some instances it may be a week or more before the other side enlarges, or only one gland is affected. All grades of intensity are seen, and there are light cases which could be termed abortive. In these there is slight fever with a little tenderness and swelling which disappears in three or four days. The average case presents a large rounded swelling at the angle of the jaw, with the lower edge of the lobe of the ear as its centre. The swelling is somewhat boggy at first but does not pit on pressure. Later it becomes very tense, rather firm, and the skin over it is stretched and glazed. In some cases there is a little redness, most marked just back of the ear, while in others there is a considerable blush of the skin and exceptionally an almost erysipelatous redness. There is an area of 1 to 2 mm. redness about the opening of Steno's duct and there is swelling so that the opening extends beyond the mucous membrane (Cowie's duct sign.)

In the most severe forms, which are rather rare, there may be enormous swelling and œdema of the tissues which may extend all around the neck and head and as far as the outer end of the clavicle. These patients present a grotesque, unrecognizable appearance.

The *submaxillary* glands may be affected after the parotids. In some cases the submaxillary glands alone, or the submaxillary and the sublingual glands, may be attacked without any involvement of the parotids. The sublingual glands are less commonly affected, although they may be attacked after the parotids or by themselves. The sublingual tissues may be involved without any distinct glandular involvement.

Pain is almost a constant symptom, although exceptionally absent. It is located in the swollen gland, back of the jaw, in the temporo-maxillary articulation, and often down the neck. The pain is increased on pressure, mastication, and salivation, and is rendered acute by taking acids; as lemon juice or vinegar, into the mouth; and even the sight of them may cause pain in neurotic subjects.

The throat cannot be said to be involved except in severe cases, when there may be swelling due to the œdema. The tonsils may be pushed inward by this and if large may render swallowing very difficult. Some have described an enanthem, but this is a complicating stomatitis.

Fever is nearly always present. It may precede the swelling or come on about the same time, and usually ranges from 102° to 103° F., but may be much higher. It disappears as the swelling subsides or sometimes several days before. After an attack of mumps there may be a subnormal temperature for some days. The jaw is usually stiff and in some cases the trismus may precede the swelling. The saliva may collect in the mouth owing to increase in the secretion and the difficult or painful swallowing, while in other cases there is a decrease in the saliva and consequently a dry mouth. In unusual cases there may be little or no pain, fever, or constitutional disturbance, and the swelling in such cases is usually slight.

Complications.—These are numerous and vary greatly in different epidemics. In one epidemic one particular complication may be quite frequent, as epistaxis, while in other epidemics another complaint, as abdominal pain or diarrhœa, may be common.

Metastasis.—Other structures of the body may be involved, most frequently the testicle in the male, and in the female, the breasts, ovaries, and labia majora. Swelling of the inguinal glands occurs in both sexes.

Orchitis.—Exceptionally this may occur before the parotids are affected; instances have been recorded where in epidemics it was the only lesion. As a rule, orchitis begins at the time when the parotid swelling is subsiding; but it may come on after the parotid swelling has disappeared entirely. There is a return of the fever and constitutional symptoms, and these latter are often severe, although occasionally absent. The testicle swells, becomes tender and painful, and the swelling continues for three to five days or longer and then subsides. Following such an attack there may be atrophy of the testicle. Orchitis is uncommon in infancy and not often seen until puberty or later. Ovaritis occurs in the same way. There is pain in the pelvic region, with swelling and tenderness of the ovary, and this lasts about the same length of time as orchitis. The breasts may become swollen, hard, and painful, and males as well as females may be affected. The prostate may be involved and cases of urethritis have also been reported. Other glands may occasionally be affected, as the thyroid, which becomes swollen and tender. There may be swelling of the lacrymal glands.

Pancreatitis.—The symptoms come on between the first and the twelfth day, usually between the third and the sixth, and last from two to seven days. There is pain between the xiphoid cartilage and the umbilicus, sometimes radiating along the costal arches and to the back. There is pain in the epigastric region on pressure and at times nausea, vomiting, and diarrhœa. Tenderness over the pancreatic region is not an uncommon occurrence in the course of mumps.

Eye.—These are chiefly of an inflammatory nature, with the usual symptoms. External œdema about the eyes with marked chemosis may render the patient well-nigh unrecognizable.

Ear.—The most frequent is deafness, and in about half the cases it is bilateral. There may be tinnitus and sometimes other symptoms. If the deafness is due to a central disease the prognosis is bad. Usually the deafness comes on about the fourth or fifth day, but sometimes as late as the tenth or even the fifteenth day.

Nervous System.—Symptoms resembling meningitis may come on and may follow orchitis. There is an increased lymphocyte cell count in the spinal fluid and globulin, sometimes absent early, is eventually present. Complete recovery is the rule, but paralysis, aphasia and other sequels may occasionally be noted. Facial paralysis has been reported as have paraplegia and pseudo-tabes due to neuritis.

Respiratory Tract.—Inflammatory conditions of all parts of the respiratory tract occur, such as coryza, bronchitis, congestion of the lungs and lobar or bronchopneumonia. Œdema of the glottis may be a dangerous complication.

Cardiac.—Following the attack there may be a slow or intermittent pulse and with this a low temperature and syncope. Endocarditis and pericarditis are rare.

Renal.—Acute nephritis generally ending in recovery may be noted and occasionally chronic nephritis follows an attack of mumps. It generally appears early in convalescence but it may be four or five weeks after the attack before it manifests itself. Acute symptoms referable to the kidneys have been noted coming on with the onset of the swelling of the salivary glands.

Joint Symptoms.—Occasionally there may be pain or swelling of the joints and bursæ. Septic arthritis with suppuration has been reported, but should lead to a doubt as to the correctness of the diagnosis.

Blood.—Pick reports the blood findings in mumps to be a slight relative increase in the mononuclears at the height of the disease, but no leukocytosis.

Diagnosis.—This is as a rule easy—the history of exposure, with a large swelling, the centre of which is the tip of the lobe of the ear, usually suffices. It is differentiated from enlarged lymphatic glands by the position of the swelling, as in mumps the little hollow between the mastoid and the jaws is completely filled, while in adenitis the swollen gland is lower down. Non-specific parotitis frequently suppurates, especially if it occurs in pyemia.

Other Forms of Parotitis.—One should bear in mind that swelling and tenderness of the parotid may occur from numerous causes other than mumps. These non-specific enlargements may be classified as follows:

(*a*) Following or during *infectious* diseases. Typhus fever, typhoid, pneumonia, scarlet fever, and diphtheria, may be especially mentioned; but swelling of the gland may occur in any infectious disease and suppuration is very common. It is not very rare with syphilis.

(*b*) From *septic infections*, most commonly after pelvic and peritoneal inflammations, appendicitis, cystitis, and pyelonephritis. In these cases the affection may be sympathetic or due to infection.

(*c*) Following disease or injury of the *abdominal* or *pelvic organs*, and rarely from operations upon other parts of the body. The submaxillary and sublingual glands may also be affected. Bucknall gives the following list of operations which have been followed by parotitis, even though the operation was entirely aseptic: Exploratory laparotomy, gastrotomy, and other operations upon the stomach; enterectomy, colotomy; hernia operations; ovariotomy; operations upon the uterus and tubes; renal operations; operations on the liver and gall-bladder. To this list may be added castration, or operations on or injuries of the testes, the insertion of a pessary, the passage of a catheter, excision of hemorrhoids, and amputation of the leg. Delivery, abortion, menopause, or disorders of menstruation may be followed by parotitis.

(*d*) In *chronic diseases*, as diabetes, and any grave form of asthenia, and in general paresis.

(*e*) In *chronic poisoning*, as that due to mercury, lead, or the iodides.

(*f*) In association with facial paralysis.

(*g*) In Mickulicz's disease, in which there is enlargement of the salivary and lacrymal glands, coming on without any apparent cause.

(*h*) In gaseous tumors of Steno's duct as are seen in glass-blowers.

Prognosis.—As a rule this is good. Occasionally one of the complications leaves a permanent lesion behind it; deafness is one of the most

frequent. Suppuration rarely occurs. The cases in which suppuration and gangrene have been reported are either not mumps or are due to accidental infections. Stewart reported a death from syncope on the fifth day, previous to which the breathing had been asthmatic. Atrophy or a lack of development of the testicle may follow orchitis. This is usually only upon one side, but it may in some instances be bilateral. In these latter virility is usually retained.

Protective Therapy.—Hess has suggested the use of injections of 6 to 8 cc. of blood from children convalescent from mumps injected intramuscularly and claims good results.

Treatment.—Mumps is a self-limited disease, little influenced by treatment. Much can be done, however, to make the patient more comfortable and to relieve pain. The food should be liquid or soft and acids and highly seasoned foods should be avoided. A mouth-wash should be used to keep the mouth clean, as brushing the teeth may be impossible. The external application of heat is grateful to many patients. The swelling should be anointed with an ointment or a glycerin application to render the stretching of the skin less disagreeable. Various medicaments are mixed with these. Five per cent. guaiacol in an ointment, or glycerin may be used. Belladonna is highly recommended. Methyl salicylate may be applied to the gland three or four times a day. Internally a dose of calomel or a saline should be given at the onset, and the bowels kept open during the attack. Anodynes may be given if necessary. Tonics, especially iron, may be used during convalescence.

In case of orchitis it is advised to incise the tunica albuginea either by a long cut or an H-shaped incision. This relieves the tension and prevents atrophy and loss of function.

CHAPTER V.

TYPHUS FEVER

By THOMAS McCRAE, M.D.

Definition.—Typhus fever is an acute disease, occurring in epidemics or sporadically, characterized by a sudden onset, high fever, a macular-papular eruption, toxemia, and a comparatively definite course usually terminating by crisis. The disease is conveyed by the body louse and perhaps also by the head louse.

The work of recent years has added materially to our knowledge of the disease and many of the accepted views regarding it have to be revised. The disease is more widespread than was thought and with singular complacency many of us have looked at it without seeing it. It occurs not infrequently in the eastern cities of the United States and probably is commoner than we even now realize. This mild sporadic form with a low mortality is comparable to the mild forms of smallpox. Experimental work has shown that the disease can be transmitted to monkeys, that the form described by Brill is identical with Mexican typhus, and that the infection is carried by lice. This last obervation explains many puzzling features; for example, the decrease of the danger of infection when the patient was removed to a hospital and the great danger to attendants in epidemics. The conveyance of the disease by the body louse has been definitely proved by the infection of monkeys, and it seems possible that the head louse may also act as a carrier (Anderson and Goldberger). It is a disease rather of temperate and cold climates; Great Britain, Ireland, and Russia have suffered especially from it. How many unrecognized cases occur it is impossible to say. The disease is more or less endemic in Great Britain and Ireland, but it is well controlled and there is no danger to the community. It is comparatively frequent in Mexico. In certain parts of Europe, especially the southeast, the disease smoulders, and in certain of the Baltic and Polish provinces, in Hungary and Turkey, it is always more or less present. Southern Italy is also a focus and in northern Africa it is apparently endemic. The Great War gave typhus fever an opportunity to show its powers and the epidemics and mortality were appalling in their severity, especially in southwestern Europe.

Etiology.—Many organisms have been described. The weight of evidence seems to support the view that *Rickettsia prowazeki* is the causal agent.[1] The disease is conveyed by the body louse but lice do not invariably become infected when fed upon typhus fever patients. The *Rickett-*

[1] See *The Etiology and Pathology of Typhus Fever* by Wolbach, Todd and Palfrey, 1922. This is the report of the Red Cross Typhus Research Commission to Poland and gives an excellent study of the problem of etiology.

sia prowazeki is found in the feces of the louse and infection may result from scratching. The relationship of the Weil-Felix reaction is puzzling. This consists in agglutination of *Bacillus proteus X* 19 by the blood of patients with typhus fever. While valuable in diagnosis there is no suggestion that the proteus bacillus is the causal organism. There are varying opinions as to the time of greatest infection, many of the English writers holding that the danger of contagion is slight during the first week, while Curschmann believed that it is greatest at the beginning and height of the febrile stage. The virus is apparently present in the blood during the entire febrile period and for a day or two afterward in the experimental cases in monkeys.

Sex and Age.—In widespread epidemics the two sexes are equally attacked, but in districts where the disease exists for some time in partial epidemic form, males are in the majority. Infants are apparently only slightly susceptible but after the age of five years children appear to be almost as much so as adults. The number of adults over fifty years is comparatively large. Among 7741 cases (Curschmann) there were 12.8 per cent. below fifteen years, 65.2 per cent. from fifteen to forty, 18.7 per cent. from forty to sixty, and 3.2 per cent. over sixty years of age.

Social Conditions.—These play a most important part and those living in insanitary and crowded dwellings are most likely to be infected. Knowing the method of conveyance the reason for this is evident and for the association of the disease with privation and poverty.

Morbid Anatomy.—The skin usually shows some evidence of the rash and sometimes gangrene. The disease affects particularly the bloodvessels of the skin, central nervous system and to a lesser degree those of the viscera. The *Rickettsia prowazeki* localizes almost exclusively in the vascular endothelium. The resulting changes are degenerative, causing thrombosis in the vessels, and proliferation in the endothelial cells and neuroglia. Rigor mortis is usually slight and disappears rapidly. Putrefaction occurs rapidly. The muscles are soft and on section have a deep red color, with hemorrhages into their substance in some cases. Histologically they show marked degeneration, which may be especially marked in the heart muscle.

Nervous System.—Occasionally there is marked injection of the bloodvessels of the meninges and brain. "Nodules" are found widely distributed in the central nervous system but mostly in the medulla and pons, associated with the bloodvessels, and are regarded as characteristic. The lesions are sharply circumscribed and are composed almost entirely of neuroglia cells. Death probably often results from extensive involvement with these nodules.

Respiratory Tract.—The mucous membrane of the pharynx and larynx commonly shows an inflammatory condition with perhaps superficial erosions. The changes about the pharynx may be quite marked and at times perichondritis with necrosis and pus formation is seen. In the trachea and bronchi the mucous membrane is inflamed and at times shows hemorrhages. With the bronchitis there is frequently bronchopneumonia and collapse, while hypostatic congestion is common. Lobar pneumonia varies in different epidemics.

Circulatory System.—The heart very commonly shows some amount of dilatation with degenerative changes in the muscle. The distinctive focal lesions are common in the myocardium.

Digestive Tract.—There are no distinctive lesions in the stomach and intestines. There is no change in the Peyer's patches, although in some cases the follicles in the intestine may show some swelling. The mesenteric glands are not enlarged. Ecchymoses may be found on the peritoneum. The *liver* may be enlarged, soft, and hyperemic. There is a constant diffuse reaction in the cells of the reticulo-endothelial system.

Spleen.—The condition depends on the day of disease when death occurred. If during the first week, the spleen is usually enlarged, but after the middle of the second week this is usually not found. On section the spleen is dark red and the pulp is soft.

Genito-urinary Organs.—The kidneys are usually swollen, hyperemic, and show cloudy swelling. Acute nephritis is fairly common.

Skin.—The changes are constant and characteristic, showing vascular lesions and perivascular accumulations. The first change is swelling of the endothelium of the capillaries and small vessels. Thrombi form in the arteries and veins of the lower part of the corium. Groups of cells form about the vessels, forming the "nodules." There is a diffuse perivascular infiltration and hemorrhage into the corium by the eighth day.

Symptoms.—Incubation.—This is usually considered to be between eight and twelve days but limits of four to fourteen days have been observed. The instances of very short incubation periods are doubtful. During this period there may be general malaise, slight headache, and anorexia.

Onset.—This, as a rule, is abrupt, with headache, general pains, and frequently one or more chills or occasionally chilly sensations only. With the sudden onset there is usually high fever and great prostration, often so marked that it is rare to see a patient who has kept about longer than the second day, while the majority give up on the day of onset. The chill may be repeated and there may be nausea or vomiting. The general appearance at this early stage is often suggestive; the expression is dull and heavy with the face very red and the conjunctivæ showing marked congestion. The tongue is dry and tremulous. The temperature usually rises rapidly and may reach its maximum on the second or third day. With this there may be very severe headache but the patients rarely have much delirium, although they may show the ordinary febrile confusion. In severe attacks or in alcoholics there may be delirium almost from the onset. The abdomen shows no special features except that the spleen is generally enlarged early.

About the third to the fifth day the *eruption* appears, first on the abdomen, then on the chest and shoulders, then over the back and extremities. The face becomes red and swollen but rarely shows the characteristic eruption and the palms of the hands and the soles of the feet usually escape. The rash usually requires from forty-eight to seventy-two hours for its full development. At first the rash is macular, the areas being sharply defined, pink and disappearing on pressure. During this period the patient usually shows marked mental disturbances and the

delirium is often of a violent type. He should be watched carefully as he may jump out of bed and endeavor to escape or attack the attendants.

The eruption changes, a certain number of the spots becoming hemorrhagic, and with this the rash becomes much more prominent and has a dirty, bluish color. If with this there be extensive subcutaneous hemorrhages, the skin assumes a curious dusky appearance, which is usually seen about the beginning of the second week. There may be a blotchy erythema in addition. After this the picture changes somewhat, the patient becoming very weak, apathetic, and lying in stupor or coma vigil. There may be difficulty in swallowing and incontinence of urine and feces.

Throughout the attack the temperature continues high, being ordinarily about 104° F. to 105°. The pulse is usually frequent and toward the end of the attack becomes small and weak. In rare cases the rate is low, which is a grave sign. Toward the latter part of the second week, if the patient recovers, the fever disappears. Despite the usual description of the termination being by crisis, in the majority the termination is by rapid lysis and occupies about two days. A defervescence which lasts for four or five days should suggest some complication. Toward the end of the disease the enlargement of the spleen disappears and the skin lesions, with the exception of the petechiæ, disappear before the defervescence. The petechial lesions usually show desquamation and remain as brown or yellow spots. With the termination of the fever the skin becomes moist and there may be profuse sweating. Recovery is often very rapid.

Temperature.—This usually rises very rapidly, may be at 104° F. on the evening of the first day and reach the maximum on the evening of the second day. The remissions are usually slight and the curve shows little change until the latter part of the second week, when it begins to drop in the evening. In certain cases there may be a drop at the end of the first week but this is not constant. In the milder cases remissions may occur in the second week and occasionally precritical drops.

Defervescence.—This occurs usually from the twelfth to the fifteenth day, rarely from the sixteenth or seventeenth. The temperature curve is much like that of the onset and may be with a sudden drop of perhaps 8° in a few hours, but in the majority it occupies a period of about two days. In some cases with a comparatively mild course defervescence is protracted, or in mild cases the temperature may show many variations. Defervescence may occur about the end of the first week or be unduly prolonged. In certain fatal cases there is a high temperature before death, while in others there is a fall to below normal, usually with a very rapid pulse and great prostration.

The Rash.—This is most important, as on it in many cases the diagnosis must rest and it is practically the only characteristic sign. The eruption may appear from the second to the seventh day but most commonly on the fourth or fifth, and this may vary in different epidemics. An erythematous rash has been described as occurring before the typical one. The eruption consists of two elements: (1) A rash much like that of measles, and (2) the characteristic macular petechial eruption. The first may

appear before the roseola or with it and is especially likely to occur on the chest and abdomen, forearms and legs. It has been termed a mulberry rash and presents a dusky red mottling, which has been described as seeming to be below the surface of the skin. It may disappear before the end of the attack. The specific rash usually appears first on the abdomen and then about the chest and shoulders. After this it appears on the extremities, while the eruption on the trunk continues to increase in number. The whole rash is usually out within forty-eight hours and a second crop is practically unknown. The face rarely shows the eruption. The number of spots is very variable and bears no relation to the severity of the attack. As a rule three distinct stages may be observed: (1) A simple hyperemia; (2) a stage when hemorrhage is occurring into the eruption; and (3) typical petechiæ. The fresh spot is a red macule which disappears on pressure and as a rule is not raised so much as the rose spot of typhoid fever. The outlines are more or less irregular and in dark-skinned individuals they may be difficult to recognize. The eruption may not develop beyond this stage in mild cases.

In the next stage the spots become darker, have a dirty reddish color, and do not disappear entirely on pressure. This is due to the hemorrhagic change which usually begins at the centre and extends to the periphery of each spot. The number of spots which undergo this transformation varies in different patients; there may be only a few or they may be so general that they give a curious appearance. These areas are often most numerous in the inguinal region and over the back. The hemorrhagic change must be distinguished from an additional petechial eruption, exactly comparable to what may occur in other infections. These petechiæ are likely to appear in the latter part of the disease and if abundant are of grave import. They are analogous to the hemorrhagic eruption which may occur in measles. A slight hemorrhagic eruption in alcoholics is less important.

The duration of the hyperemic eruption is short. If there be no hemorrhagic change, the spots usually disappear by the second or third day, and if the hemorrhagic change is slight the spots persist for from four to six days. When the typical eruption is present the duration is usually from seven to ten days.

There are other eruptions among which is a miliary rash, which may be present late in the attack and is of no special significance. As a rule distinct desquamation is seen after this but it may occur without the presence of sudamina. Herpes may be present and Curschmann noted them in 5 per cent. during one epidemic. Boils and bed-sores are not common. In severe attacks, particularly if there has been marked hemorrhage into the skin, there may be areas of necrosis, sloughing and gangrene. Sweating may occur toward the crisis but is not often profuse.

Nervous System.—The symptoms of involvement of the nervous system are usually marked. Headache is very common, almost constant early in the attack, and with it there may be vertigo and general pains. At the onset the mental condition is usually clear, although the patients may be rather dull and show slow cerebration, while insomnia is common. As the disease progresses the mental features become more marked in one

of two ways—either violent delirium or marked apathy or almost coma. The delirium is rather of a violent type. The patients are usually very restless and may become violent. Thus one patient seen by the writer suddenly jumped out of bed, overpowered the orderly and put his fist through a strong wire screen over the window, cutting his arm severely. The appearance of the delirious typhus fever patients is often characteristic and in marked contrast to the delirious typhoid fever patients. They are curiously alert, seem to be watching what is going on around them, frequently try to get out of bed, and with the flushed face and bright eyes present a striking picture. The onset of severe delirium early in the disease is of bad omen. In other patients coma predominates. They are much prostrated, lie quietly in coma vigil and take no note of their surroundings. With this there may be marked tremor, a rapid, feeble pulse, and in some instances the patient is practically in collapse. Coma may persist after the temperature is normal.

Tremor.—Tremor is a common severe manifestation and may be only slight or so general and severe that it suggests a convulsion. Subsultus tendinum with picking at the bedclothes is common. Actual convulsions have been noted. These severe nervous manifestations are associated with a grave prognosis. Sensory disturbances are sometimes troublesome at the onset and may occur in convalescence.

Meningitis has been reported. Hemiplegia has occurred but is rare and is due to meningeal hemorrhage or to embolism or thrombosis. Neuritis may occur but is evidently not common.

Special Senses.—Marked injection of the conjunctivæ is common. Hemorrhages into the conjunctivæ may occur and in some patients with marked coma vigil there may be ulceration. Disturbances in hearing are not uncommon and apparently largely due to hyperemia; otitis media may occur.

Respiratory Organs.—Epistaxis has been noted early in the disease. A catarrhal condition of the nose and pharynx is common at the onset, frequently extends down the trachea and bronchi, and causes an irritative *cough* with which there may be little expectoration. In some cases more serious changes may occur, such as erosions, fissures, extensive ulceration, and œdema. These are always of grave import, both in themselves and from the danger of pulmonary infection, while, should the patient recover, permanent changes in the larynx are common. In the lungs there may be bronchopneumonia, hypostatic congestion, or lobar pneumonia, all of which are serious. Pleurisy is not infrequent and if with pneumonia, empyema may follow.

Circulatory System.—With the toxemia there may be myocarditis and some dilatation. The pulse early in the disease is usually rapid, small, and of low tension. In the second week the pulse becomes small and at times irregular. A slow pulse is occasionally seen. The heart sounds show considerable change, the first becoming much like the second and later in the attack disappearing entirely.

Leukocytosis generally occurs. Love reports the average for 26 cases as 24,000, with an increase specially in the polymorphonuclear cells. He noted that in the blood of the fatal cases no eosinophiles were present

but they were never completely absent in the blood of the non-fatal ones and considers that the absence of eosinophiles means a grave prognosis. In the non-fatal cases there was usually a slight increase in the large mononuclear elements. There was usually an increase in the leukocytes after the appearance of the eruption.

Digestive Tract.—The tongue is usually furred, and as the disease progresses, it and the lips are likely to become fissured and covered with sordes. Gastric disturbances do not often occur. The bowels are usually constipated, although there may be diarrhœa. If the rash be of marked hemorrhagic type it is quite possible that there may be hemorrhage into the intestine, but such cases are rare. Jaundice has been noted during the second week, and is probably toxic.

Genito-urinary Organs.—Changes in the kidney are such as may occur in any acute febrile disease and albuminuria is common. In rare cases there may be a definite nephritis, which is always serious. Orchitis is rare. Menstruation is usually suspended during the attack, although occasionally it may occur with the onset. With pregnancy the danger of abortion is probably less than in other severe acute diseases and it is less likely to occur during the later months of pregnancy.

Variations.—There may be great variation from the usual course, as is true of all acute infections. In some patients the attack is so short that the recognition offers great difficulty. A group of abortive cases is described which begin with severe symptoms, the temperature being high at first and then falling rapidly. Somewhat like these is a group of cases seen especially in physicians and nurses who are handling patients with the disease, in whom there are symptoms suggestive of toxemia. They usually recover quickly as soon as they are removed from contact with patients. Malignant attacks are seen, especially in epidemics, with death on the second or third day. Hemorrhagic cases occur as in other acute infections.

The mild form prevalent in the United States differs somewhat from the severe epidemic form and it is important to know its characteristics. We are indebted to Brill[1] for a complete description of its features. The onset is usually sudden with a chill or chilly sensations, followed by severe headache and general pains. Fever appears quickly, reaches the maximum by the third day and is fairly constant (usually 103° to 104° F.). Prostration and apathy are marked. The eruption appears on the fifth or sixth day, is usually profuse on the body and extremities and comes out in one crop within a period of twenty-four hours. It is a macular-papular rash of an erythematous character, dull red in color, occasionally petechial, and usually not entirely obliterated by pressure. It persists until the end of the attack. It may easily be regarded as an unusually profuse, bright typhoid fever rash.

During the height of the attack the patient is quiet, looks ill, has a flushed face and congested eyes, and severe headache. Bronchitis is fairly common. The pulse is not as rapid as might be expected from the fever. The tongue is coated; constipation is the rule; the spleen is usually

[1] *Am. Jour. Med. Sci.*, 1910, **139**, 484; and 1911, **142**, 196.

enlarged. There is slight leukocytosis (9000 to 11,000). Blood cultures are negative. The termination is usually by crisis after a duration of twelve to fourteen days. The mortality is low.

Relapse.—This is exceedingly rare and for ordinary purposes the probability of its occurrence may be disregarded. Among 18,268 cases in the London Fever Hospitals there was only 1 case of relapse.

Association with Other Diseases.—There are rare instances in which typhus fever coëxists with one of the acute exanthemata, but some of these may be instances of the rapid succession of one infection after the other. There are instances of a patient with typhoid fever being sent by mistake into a typhus ward and contracting the disease. Diphtheria may coëxist, but in the absence of definite bacteriological findings the diagnosis is doubtful, owing to the frequent occurrence of membrane over the pharynx in typhus fever. Relapsing fever and typhus fever have been noted as coëxisting. Some consider that chronic alcoholics are prone to contract the disease and that the course is usually more severe, as they show severe nervous manifestations, while cardiac failure and renal changes are common.

Convalescence.—This is usually rapid and as a rule the nervous symptoms disappear with defervescence, although delirium or mental confusion may persist for a few days. True psychoses are rare. Subnormal temperature is common during the first week of convalescence and the pulse may continue rapid; bradycardia sometimes occurs. Neuralgia is said to be fairly common.

Prognosis.—In slight epidemics the death-rate may not be higher than 10 or 15 per cent., while under unhygienic conditions it may rise to 20, 30, or 50 per cent. In hospitals during epidemics the average mortality is from 20 to 25 per cent. Murchison's series of 18,592 cases showed a mortality of 18.78 per cent. In the American cases the death-rate is very low, about 1 per cent. The effect of age is marked; thus in children below the age of five years the death-rate is high but from ten to fifteen years is low, while over the age of fifty it is high. The position in life influences the mortality, for those who have been living under poor sanitary conditions or in crowded surroundings are more likely to die. The influence of overexertion is of interest, for in epidemics a large proportion of the physicians, nurses, and attendants who take the disease die of it. The conditions under which the patient are treated influence the mortality. The death-rate is lower if they can be removed to a good hospital.

The form of severe infection spoken of as *typhus siderans* is almost always fatal, death occurring by the third or fourth day and perhaps even before the rash is completely out. The hemorrhagic form usually ends fatally, although if the hemorrhagic process makes its appearance late, the prognosis is more favorable the later it appears. With hyperpyrexia the prognosis is usually grave, although a high temperature early in the attack is not of especially bad omen but its persistence is serious. The condition of the circulation is important, the pulse is rapid early in the disease, as a rule, but if with this it be soft and easily compressible or irregular, the outlook is grave. The appearance of pulmonary com-

plications is serious, especially in the older patients. A diminished amount of urine, the presence of large amounts of albumin and especially an acute nephritis are of serious import. The early onset of severe nervous manifestations is a grave matter, while coma vigil with much muscular tremor means severe intoxication.

Diagnosis.—In an epidemic this is likely to offer comparatively little difficulty, but when cases arise sporadically, immediate recognition may be very difficult, as is true of any acute infection which the profession has little opportunity of seeing. The mistake of considering other disease as typhus fever is most probable during epidemics; with sporadic cases or the early ones of an epidemic we are more likely to make the opposite error and mistake typhus fever for some other disease.

Weil-Felix Reaction.—The agglutination of *Bacillus proteus X* 19 occurs in the great majority of cases. In some cases agglutination occurs in high dilutions, from 1 to 800 to 1 to 3200.

At Onset.—The onset may offer points of resemblance to several of the acute exanthemata, especially smallpox, scarlet fever, and measles. Relapsing fever, meningitis, and septicemia may give difficulty. In the acute exanthemata we may have the same sudden onset with a rapidly rising fever, severe headache and marked prostration, and until the eruption appears a diagnosis may be impossible. In the recognition of *smallpox*, the occasional, early scarlatiniform rash is important, while the characteristic rash of smallpox usually occurs on the face early in the attack, while in typhus fever the face is usually not involved. The drop in temperature with the appearance of the rash in smallpox may be of assistance. There may be special difficulty in the differentiation of the hemorrhagic form, as it may end fatally before the characteristic rash appears. There may be the same difficulty in distinguishing the disease from scarlet fever or measles. In doubtful cases care should be exercised before a positive diagnosis is made and in certain instances it is necessary to wait.

Relapsing fever may cause difficulty, especially as the diseases arise under the same conditions, but examination of the blood and the subsequent course should make the diagnosis clear in a short time. The coëxistence of the diseases has to be kept in mind. *Cerebrospinal meningitis* may suggest typhus fever, especially if there be a rash with it, but lumbar puncture will usually render its diagnosis clear. *Septicemia*, and especially the type with a latent endocarditis, may give great difficulty. The result of blood-cultures may be positive, but in some cases it will probably be necessary to observe the patients for several days before a positive diagnosis can be made. Plague may give difficulty and also perhaps pneumonia at an early stage. In malarial fever, certain forms of purpura and typhoid fever with a sudden onset, careful examinations and continued observation should soon give the diagnosis. Uremia, probably with a severe terminal infection, has been confused with this disease. With a sporadic case of typhus fever the diagnosis before the appearance of the rash will be most difficult and can rarely be made with any certainty.

In the Stage of Eruption.—In typical cases this is not likely to offer much difficulty, which is true of disease generally, as it is the atypical cases that give the difficulty and for them no definite rules can be given. The diseases which have to be especially considered are typhoid fever, measles, purpura, and some of the other acute infections. The rash of typhus fever may show great variation from the usual descriptions, and it is such cases that offer the greatest difficulty in diagnosis from typhoid fever. This is particularly true of the sporadic form in the United States. The onset of *typhoid fever* is usually more gradual, the early symptoms very much less severe, and it is rare to have severe nervous manifestations early in the course. Prostration occurs early in typhus fever. The pulse in typhus fever is much more rapid early in the disease and is rarely dicrotic. Enlargement of the spleen is common to the two diseases but appears early and disappears early in typhus fever. As a rule there is no leukocytosis in typhoid fever and the result of blood cultures or the Widal test may make the diagnosis positive. The eruption in typhus fever is usually at first only hyperemic and not hemorrhagic and the number of areas that become hemorrhagic may be few, while on the other hand a certain number of the rose spots in typhoid fever may become hemorrhagic. The typhus rash is common on the arms and legs which is rare in typhoid fever. The rash of typhus fever appears much earlier than that of typhoid fever and in one crop, while in typhoid fever there are successive crops. In typhus fever the eruption is fairly even over the body and extremities. The general appearance is often suggestive. The curious wild look with swollen, red face and injected eyes (sometimes termed the "ferret eyes") of the typhus patient is in contrast to the ordinary dull, stupid appearance of the one with typhoid fever.

The rash of *measles*, especially early, may be much like that of typhus fever, and if in the latter disease the measles-like eruption, sometimes present, is marked, there may be great difficulty. The face is generally attacked first in measles, while as a rule it escapes in typhus fever. The appearance of petechiæ should make the diagnosis clear. Careful examination should always be made for Koplik's spots. In measles with or soon after the appearance of the eruption there is usually a drop in the temperature, which does not occur in typhus fever.

Purpura is not likely to give difficulty for any length of time. Insect bites in patients who are suffering from fever may cause difficulty, but careful examination of the lesions will probably show the bite in the centre. A copaiba rash has been mistaken for that of typhus fever. Anthrax and glanders have given difficulty in rare instances.

Prophylaxis.—Wherever possible the patients should be removed to hospitals. In an epidemic it is best to treat the patients in temporary barracks or tents. It is important in epidemics to carry out periodical careful inspection of crowded districts and unsanitary localities, so that cases may be recognized early and isolated. Knowing the method of transmission every effort should be made to kill lice. All the patients' clothing should be boiled, sterilized by heat or burned, and the room thoroughly cleaned. The hair of the head should be clipped close or shaved, and the head washed with phenol solution (4 per cent.). It is

advisable to give the patient a sponge bath with phenol solution (2 per cent.). Persons handling the patient before he is cleaned should wear proper clothing to prevent lice reaching the body. Those living with the patient should receive thorough treatment for pediculosis and all their clothing should be sterilized by heat, boiling or by phenol solution (5 per cent.).

Treatment.—We have no specific treatment. We have to deal with a severe toxemia and with certain complications, especially of the respiratory tract and circulatory system, which are to a considerable degree secondary to the toxemia. Consequently our endeavor must be to keep the patient in the best possible condition, nourish him as well as we are able, and favor the elimination of toxins. The patients should be put to bed at once and kept absolutely at rest. The diet should be fluid; milk and its modifications, albumen water, broths and eggs may all be given. It is well to feed at frequent, regular intervals, and care should be taken with those who are dull and stupid that food does not pass into the respiratory tract. Large amounts of water should be given.

Hydrotherapy, if possible in the form of the tub bath, should be carried out as in typhoid fever. In severe attacks it is well to give the tubs at a temperature of 70° F. In the patients with marked nervous symptoms it is well to use cold affusions to the head during the baths and an ice-bag or cold cloth should be kept constantly applied at other times. The use of antipyretic drugs does not seem wise. Delirium may require treatment, and while the baths are usually the best means of combating this, it is sometimes difficult to give them. In this event one may substitute packs or sponges. Delirious patients should be constantly watched. With marked delirium, severe headache, or insomnia, it may be well to give bromides and opium, but in severe cases it is better to use morphine hypodermically. Careful attention should be paid to the nose and mouth and they may be irrigated or washed with an alkaline antiseptic solution. If signs of laryngeal involvement appear, the patient should be carefully watched so that if œdema of the glottis comes on, tracheotomy may be done. The patients should be kept turned from side to side to lessen the danger of hypostatic congestion. If there be failure of the circulation, strychnine may be given hypodermically (gr. $\frac{1}{40}$ to $\frac{1}{20}$, gm. 0.0015 to 0.003), digitalis and caffeine in the usual dosage. Conditions in the other organs must be treated as they arise. The bowels should be kept open by simple purgatives.

Convalescence is usually rapid, but it is wise to keep the patient in bed for a week after the temperature is normal. If the pulse continues rapid or very slow, caution is advisable and the patient should be kept quiet for some time, as in such cases there is always the danger of syncope.

CHAPTER VI

DENGUE

By THOMAS D. COLEMAN, M.D.

Synonyms.—Dandy fever; Break-bone or Broken-bone fever; Giraffe and Stiff-necked fever; Scarlatina-rheumatica; Bouquet (corrupted into bucket-fever); Polka fever; Knockel-Koorts, etc.

Definition.—Dengue is an acute infectious disease, sharp in onset, of short duration, characterized by intense pains in the head and over the body, by a fever of two paroxysms, and by a polymorphic eruption, and terminating usually in recovery. The first accurate descriptions were given by Brylon of Java in 1779, and by Benjamin Rush of Philadelphia in 1780. Its synonyms are efforts to describe one or another of its prominent symptoms.

Etiology.—Geographical Distribution.—Epidemics have occurred in Spain, Syria, China, Australia, Egypt, the Philippine Islands, Cuba, Brazil, Central America, the southern portion of the United States, and other regions. It is distinctly limited in its spread in epidemic form to tropical and subtropical countries. When it occurs in regions outside of these zones, as in outbreaks in Philadelphia, New York, and Boston, it develops during the heated season. It spreads with greater rapidity than any other disease, save perhaps influenza, and develops rapidly in densely populated towns; it follows the sea-coasts, rivers, and lines of travel, in this resembling closely yellow fever. The ordinary limiting zones have usually been placed between 32° 47′ N. to 23° 23′ 5″ S. latitude, though these lines are more or less elastic.

Season.—Dengue is strictly a disease of warm weather, disappearing on the advent of killing frosts; but in tropical countries it may occur during any month of the year. In regions outside of the zones mentioned, it occurs only during the hot season.

Meteorology.—Authorities, almost without exception, emphasize the observation that epidemics have been noted in both dry and wet seasons. Altitude exercises an inhibiting influence, the disease following the line of mosquito distribution.

Race, sex, and *age* exert no influence. Filth, over-crowding, and unhygienic modes of living appear to favor its development. Conditions which favor the breeding of mosquitoes are important.

Exciting Cause.—The nature of the disease, the epidemics, and analogy all suggest that dengue is caused by a specific organism. Up to the present the discovery of the microörganism has not been made; it is ultramicroscopic. McLaughlin, Manson, Eberle, and Graham have described organisms; but doubt has been thrown on their conclusions. That the disease is of microbic origin and transmitted by the mosquito, probably

by the Culex fatigans, has been proved. Graham placed patients suffering with dengue in apartments which had been freed from mosquitoes and screened, and allowed healthy individuals to remain in close contact with those sick of the disease, and none of those so exposed developed dengue. He then took mosquitoes which had bitten patients suffering with dengue, and carried them to a small village at a high altitude where dengue was unknown. Two healthy persons allowed themselves to be bitten by the infected mosquitoes, and both developed dengue. The subjects were kept under mosquito nets until the symptoms of the disease had disappeared, and the mosquitoes were killed with the result that no other cases of dengue developed.

Graham inoculated a human subject with a solution made from the salivary glands of infected mosquitoes, with the result that the patient had a chill on the third day, and went through a typical attack of dengue. Ashburn and Craig in their work on dengue in the Philippine Islands, made valuable additions to our knowledge of the disease. Their conclusions are as follows:

1. No organism, either bacterium or protozoön, can be demonstrated with the microscope in fresh or stained specimens of dengue blood.

2. The red blood count in dengue is normal.

3. No characteristic morphological changes occur in the red or white blood corpuscles.

4. Dengue is characterized by a well marked leukopenia, the polymorphonuclear leukocytes being decreased, as a rule, while there is a marked increase in the small lymphocytes.

5. The intravenous inoculation of unfiltered dengue blood into healthy men is followed by a typical attack of the disease.

6. The intravenous inoculation of filtered dengue blood into healthy men is followed by a typical attack of the disease.

7. The cause of the disease is, therefore, probably ultramicroscopic.

8. Dengue can be transmitted by the mosquito, *Culex fatigans Weid*, and this is probably the most common method of transmission.

9. No organism of etiological significance occurred in blood cultures.

10. The period of incubation in experimental dengues averages three days and fourteen hours.

11. Certain individuals are absolutely immune to dengue.

It is doubtful how many varieties of blood-sucking insects can transmit the disease. Graham's experiments suggest *Culex fatigans* as the intermediary but Cleland and Bradley in Australia believe that the Culex rarely if ever transmits the disease, and that the *Stegomyia fasciata* is the main agent. This genus and *Aedes egypti* are the same. The following are some of the conclusions drawn by Cleland and Bradley.

1. Dengue fever in Australia is undoubtedly an introduced disease. It has been existent from time to time in epidemic form since 1885.

2. It is possible that under the single term "dengue" more than one disease is at present included.

3. Epidemic dengue in Australia is approximately coëxtensive with the known distribution of *Stegomyia fasciata*. It does not extend beyond the area in which this mosquito is prevalent.

4. *Stegomyia fasciata* mosquitoes caught in a dengue-infected district in the surroundings of cases of the disease, and some known to have fed on a dengue patient on the first and second days of his illness, transported to a non-dengue district, reproduced the disease in 4 out of 7 persons on whom biting experiments were conducted.

5. Blood taken from 3 of these 4 patients reproduced the disease when injected into other persons. The blood of 1 patient was not tested.

6. The blood of patients suffering from an attack of dengue can reproduce the disease when inoculated subcutaneously into healthy persons. The disease thus inoculated is typical in every way of dengue fever naturally contracted.

7. Results of the inoculations show that: (*a*) The virus of dengue is present in the blood as a whole. (*b*) The serum of clotted, infective blood may contain the virus. (*c*) With washed corpuscles 1 apparently positive result was obtained out of 3 experiments. (*d*) The fluid part of citrated infective blood may contain the virus. (*e*) With Pasteur-Chamberland filtrates of infected serum and corpuscles, 1 positive result was obtained in 5 experiments. (*f*) The presence of the virus in the blood has been demonstrated on the second and third days of the disease. Two experiments may possibly be interpreted as showing that infective material may be present on the eighth day of the disease. (*g*) The infection can be conveyed by subinoculations from individual to individual at least to the fourth generation without the resultant disease departing from the type of the natural disease. (*h*) The disease has not been conveyed by the application of infective serum to a scarified area, nor apparently by the application of infective material by swabbing in the nostrils.

Siler, Hall and Hitchens,[1] in a carefully controlled study in the Philippines, produced dengue fever in 25 of the 42 volunteers who were bitten by *Aedes egypti* mosquitoes infected by biting patients with the disease. The experiments suggest that the mosquito is infective throughout its life. The evidence is against *Culex quinquefasciators* being a transmitter of the disease.

Immunity.—One finds the invariable observation that an attack of dengue renders the subject immune to subsequent attacks. The experimental work verifies the observation. Patients who have had dengue are immune both to the bites of infected mosquitoes and to inoculation with the blood of dengue subjects.

Pathology.—The disease has no distinctive pathology, and few opportunities for autopsies have been afforded. A localization of inflammation on the serous membranes has been observed, especially the pleura and peritoneum; Hirsh mentions serous infiltration in the vicinity of the joints and reddening of the crucial ligaments of the knee-joints.

Symptoms.—Dengue is characterized by three stages: (1) A stage of invasion lasting from two to five days, sometimes as short as twenty-four hours; (2) a stage of remission, rarely intermission, lasting from

[1] Jour. Am. Med. Assn,, 1925, **84**, 1163.

twelve hours to three days; and (3) a stage of exacerbation in which the phases of the first period are repeated, but with diminished intensity. The *incubation* period is two to five days, during which time no symptoms may appear or the patient may experience anorexia and lassitude. The attack may be ushered in by a chill or chilly sensations. The *onset* is almost invariably sudden, some patients being attacked by the pains while at work or asleep; one patient was seized in the attitude of prayer, another in going upstairs, etc. In some the initial discomfort is trivial, amounting to more or less general pains, mild nervous symptoms, and slight fever; in a larger number of cases the invasion is with marked physical and nervous manifestations. *Prostration* is intense and is constantly present. In children the disease may be ushered in by convulsions, followed by more or less delirium, and this may occur in adults.

In a typical case the attack is ushered in by a feeling of chilliness or a distinct chill; the muscular and joint pains are intense, causing the patient to assume a more or less rigid attitude. The pains in the muscles and joints are often so severe as to make him feel as if his very bones were broken, thus giving to the disease the name of break-bone fever. The pains seem to affect every portion of the body, but are generally localized in the head, back, legs and joints. The knee-joints are most commonly affected, but in some cases practically all the joints are involved. The peculiar features of the joint manifestations are, that while the pain may be intense, there is commonly an absence of swelling, and pain is not produced by pressure on the involved joints. Passive motion of the joints may be made without pain, but an effort to move the involved joints is accompanied by much suffering. Less frequently the involved joints may be swollen and pain produced by pressure and by passive as well as active motion.

Fever.—The temperature rises steadily and may reach its maximum on the second, third, fourth, or even the fifth day; commonly the third to the fifth day, not infrequently on the second. The range is from 100° to 106° F.; cases of average severity do not go above 103° to 104° F., the maximum usually being attained during the first twenty-four hours occasionally as long as three days. The patient, though depressed, is relatively comfortable. The third phase is accompanied by a *second rise* of temperature, which rarely equals the first, and in which the symptoms are not so severe. The *pulse* is usually bounding, and ranges from 90 to 140 per minute, increasing in rate with the elevation of temperature. In some cases the secondary rise of temperature is slight or may be absent.

Nervous symptoms are manifested by intense headache, photophobia, nervous depression, restlessness, general pains, and in some instances delirium.

Anorexia is nearly always present, and in some cases nausea and vomiting may be severe. The vomiting may be persistent and the vomitus may be bile-stained; if cases of this type appear when yellow fever is coëxistent, the diagnosis is much more difficult. Especially is this true when a heavily coated tongue and jaundice are present. The tongue is usually covered with a white coating but the edges and tip are free. Constipation or diarrhœa may be present, more frequently the former.

The urine is usually high colored and scanty, but is not suppressed, and rarely shows albumin and casts.

Enlargement of the lymph nodes has been noted in some cases, but is not constant.

Hemorrhages from the mucous membranes have been observed in rare instances. The countenance wears an anxious look and is congested from the initial erythema, giving it a somewhat bloated appearance, and the conjunctivæ are congested; but neither of these is present to the extent in typhus and yellow fever.

Skin.—Two manifestations are found: the first is a vasomotor *erythema*, coming on with the onset of fever, and not essentially different from that in many of the acute infections; the second is the eruption that occurs with the second accession of temperature. The *initial eruption* varies in intensity from a simple redness to a distinct erythema, appearing on the head and trunk, and occasionally on the limbs. This causes tumefaction of the face and eyelids, which may extend to the nasal and pharyngeal mucous membranes; its duration is short. The *secondary* skin manifestation usually makes its appearance on the fourth day and is considered by many as one of the most characteristic features. While this is partly true, in a large percentage of cases the eruption is so evanescent that it escapes observation or may not appear at all, just as the secondary pyrexia may be slight or absent in some cases. Horlbeck states that in the epidemic in Charleston in 1895 this eruption occurred in 40 per cent. of all cases. The writer believes this estimate to be approximately correct.

The *eruption* is not characteristic, being described by some clinicians as urticarial; by some as macular, measly, roseolar, rubeoloid, etc. Usually, it appears first as a small, elevated, circular spot, dusky red in color, disappearing on pressure, and tending to coalesce with contiguous spots, making irregular patches, sometimes 2 or 3 inches in diameter; between these areas the skin looks normal. In some cases the entire skin is covered by a continuous red blush, giving the patient a scarlatiniform appearance. The eruption appears first on the palms and backs of the hands and extends up the arms; also on the trunk, thighs, and legs, and leaves in the order in which it appeared. *Desquamation* follows the eruption and is bran-like in character. It may continue two weeks or more but usually lasts a shorter time.

Convalescence is slow and the subsequent depression is likely to be out of all proportion to the apparent severity of the attack; it may last for weeks or months and be attended by prostration and soreness of the muscles and joints. Relapses have been noted in not a few instances.

Complications.—Hemorrhages from the nose, stomach, intestines and uterus have been observed. These are usually capillary but from the uterus they may be so severe as to lead to miscarriage. Pleurisy, pericarditis, endocarditis, meningitis, and orchitis have been described, though rarely.

Diagnosis.—The diseases with which dengue is likely to be confounded are yellow fever, malarial fever, relapsing fever, rheumatic fever, and influenza. In *yellow fever*, as in dengue, we have a disease of two febrile

paroxysms; but in dengue the pulse is accelerated in proportion to the fever, while in yellow fever the pulse-rate diminishes as the temperature rises. In atypical cases, in which jaundice is present and bile is found in the blood and urine, this sign may be absent and the pulse slow—a result which follows the presence of bile in the circulation. In yellow fever there are pains in the head, back, and limbs, but they do not compare in severity with those of dengue. The joint pains so prominent in dengue are absent or of small account in yellow fever. Nausea and vomiting are present in dengue, but not to the extent found in yellow fever. Black vomit and jaundice are frequent in yellow fever and rarely present in dengue. The nature of the prevailing epidemic and the mortality are of service in the diagnosis, but these do not aid in sporadic cases. Until the specific organism is found, sporadic and aberrant cases will give difficulty.

Malarial fever presents many points of resemblance to dengue; in both one obtains a history of anorexia, nausea, and vomiting, with pains in the head, back, and limbs. Dengue is not influenced by quinine; further, malaria does not occur in epidemics, and the periodicity of the paroxysms, with their recurrence and the plasmodium in the blood make the two diseases easily distinguishable.

Relapsing fever confuses only by its recurring febrile paroxysms, but aside from other features, the presence of the Spirillum in the blood should make the diagnosis relatively easy. In *rheumatic fever*, there are fever, prostration, and pain in the joints, but rheumatic fever may occur at any time of the year, and usually does occur when dengue cannot develop and does not spread in epidemics. In rheumatic fever, pressure on the inflamed joints causes severe pain, which is not usual in dengue. Rheumatic fever is largely a disease of the young, while dengue attacks all ages. In *scarlet fever* the nature of the rash, the inflamed fauces, the strawberry tongue, the occurrence almost always in children and at any season of the year, leave this disease and dengue resembling each other only in fever, prostration, and eruption.

Influenza can simulate dengue in the rapidity of its spread and the magnitude of the epidemics. The nervous and gastro-enteric forms of influenza present the confusing points, as the catarrhal form is easily distinguished. The nature of the epidemic, mortality, complications, time of year, and the presence of the influenza bacillus (of such value as it may be) should make the distinction.

Prognosis.—Except for some complication or accident the mortality is almost *nil*. The writer has never seen a fatal case.

Prophylaxis.—The methods employed in the prevention of yellow fever and malaria are equally applicable to this disease. To this end it is essential: (1) To screen the patient from mosquitoes, so that insects may not become infected and to screen the general population, so that infected mosquitoes may not inoculate them; and (2) to carry out all the usual methods of mosquito extermination.

Treatment.—Few disease require such early and energetic treatment; this not because the patient is really so sick, but because he thinks he is. At the onset the patient should be put to bed and kept there until the

second paroxysm is well passed, usually he does not require much urging. The *diet* should be simple and easy of assimilation. In a disease of such short duration it is not desirable to force nourishment on the patient, especially when the stomach is upset. It is well to clear the alimentary tract, preferably with calomel gr. ij to v (0.13 to 0.32 gm.), followed in six to eight hours by magnesium sulphate. Nausea and vomiting may be relieved by sipping ginger ale poured over cracked ice or by sipping champagne. A mustard plaster to the epigastrium often gives some relief. In some cases the nausea and vomiting are so intense that only morphine gr. $\frac{1}{8}$ to $\frac{1}{4}$ (0.008 to 0.016 gm.) alone or with atropine gr. $\frac{1}{150}$ (0.0004 gm.) will suffice.

The severe pains demand relief and for this drugs of the coal-tar class may be employed but should always be used with caution. Phenacetine in 5 gr. (0.3 gm.) doses, repeated at six or even four hour intervals, may be employed. When the pains are more severe, codeine gr. $\frac{1}{4}$ to $\frac{1}{2}$ (0.016 to 0.03 gm.) may be added. In some cases the pains are so intense that only a hypodermic of morphine, gr. $\frac{1}{4}$ (0.016 gm.) will suffice. Insomnia is sometimes distressing; in mild cases potassium bromide gr. xxx (2 gm.) may be sufficient; in more severe cases chloral gr. x to xv (0.6 to 1 gm.) may be added. These drugs, single or combined, may be repeated as indicated. Barbital, gr. v, (0.3 gm.) or trional, gr. x, (0.6 gm.) in hot water will often produce sleep, but are insufficient if nervousness is excessive or the pain is great, when morphine is required.

When muscular and joint symptoms predominate acetyl-salicylic acid, gr. v, (0.3 gm.), codeine, gr. $\frac{1}{4}$ (0.016 gm.) and camphor monobromate, gr. $\frac{1}{2}$ (0.03 gm.) in capsule every six to four hours, afford great relief. Where the muscular and joint pains are severe, external heat, dry or moist, affords some relief, as also rubbing with various liniments. A liniment composed of equal parts of oil of gaultheria and spirit of camphor affords much relief. The parts may be rubbed with this liniment and afterward covered with a cloth saturated with it. This may be left indefinitely and will not blister.

If the fever is high, hydrotherapy should be employed and much relief will come from it. An abundance of water should be taken to increase elimination by the kidneys. The temperature may be reduced by hot mustard foot baths and by sponging with tepid or cold water. An ice-cap to the head reduces temperature and often diminishes nervousness and delirium. The disease is self-limited, and unusual symptoms will have to be met as they arise.

Convalescence is often slow; the prostration with muscular and joint pains may continue for weeks, during which time the patient should be given a liberal diet and tonics.

CHAPTER VII

RABIES

By MAZŸCK P. RAVENEL, M.D.

Synonyms.—English, Hydrophobia, Madness; French, La rage, L'hydrophobie; German, Hundswuth, Tollwuth, Wuthkrankheit, Wasserscheu; Italian, Idrofobia, Rabbia, Lyssa.

Definition.—Rabies is an acute, specific, rapidly fatal malady, communicated to man from some lower animal. It is always an inoculation disease, that is, communicated directly through a wound usually made by the teeth, the infective matter being the saliva, which contains the virus, the exact nature of which is unknown.

Distribution.—Rabies occurs in almost every part of the world, Australia being the only country known to be exempt, owing to the rigidly enforced quarantine. It is very rarely seen in Holland, Denmark, Norway, Sweden, and Switzerland. In France, Belgium, Hungary, and Russia the disease is widespread. In the latter country it is common among wolves. It is quite common in Italy and Spain, although the official figures are small. In Germany the disease is seen mainly on the frontiers and is rare in the interior. It is quite common in China and Japan. Great Britain was practically free from 1900 until the Great War, during which rabies was reintroduced into the country. Several fairly extensive outbreaks have occurred since the war. Rabies increased in most of the countries which took part in the struggle. At the Pasteur Institute, Paris, the number of persons treated rose from 373 in 1914 to 1813 in 1919. Canada has been severely visited and rabies occurs in practically every part of the United States. Until 1909, the disease had not been reported west of the Rocky Mountains, but severe outbreaks have taken place at widely separated points on the Pacific slope. In 1908 there were 534 known infected localities in the United States, in 1911 there were 1381. In 1921,[1] fifteen states reported that the disease was increasing, while only four noted a decrease. Of 5558 animal's heads examined in twenty-nine states, 2699 or 48.6 per cent. were positive. From 1917 to 1921 inclusive, 168 deaths in man were reported. In 1922, 46 deaths were reported for the registration area.

Animals Affected.—All mammalia are susceptible, and birds contract rabies when bitten or otherwise inoculated. Dogs are most frequently affected, and to them we owe the perpetuation of the disease. It is not infrequent among wolves, foxes, hyenas, jackals, skunks, etc. In the Western States the coyote has been a prime factor in spreading the infection. Cats are rarely affected. Among the domestic animals cattle are

[1] T. F. Sellers: *Am. Jour. Public Health*, vol. **13**, No. 9.

most often affected, swine least so. It is uncommon in horses. In England it has appeared among the deer in parks. The money loss from rabies is very heavy.

Etiology.—Hydrophobia being always the result of accidental infection from some lower animal, its incidence follows closely that of rabies in the domestic animals, especially the dog, which is by far the most frequent source not only for man but for all other animals. Statistics of 16,172 persons bitten by supposedly rabid animals, collected at the Pasteur Institute, Paris, incriminate dogs in 15,021 cases, cats in 959, wolves in 14, foxes in 2, jackals in 9, horses in 32, asses and mules in 40, cattle 67, sheep 3, pigs in 12, and man in 13. The danger following the bite of a rabid animal depends on the species, and the location and extent of the wounds. The bite of wolves is more apt to be followed by rabies than that of any other animal, owing partly to the greater activity of the virus, and partly to the savage mode of attack, the wounds being extensive, lacerated, and often located about the head and face. Next in point of danger come bites from cats, then dogs, and lastly other animals. The report of the Pasteur Institute at Kharkoff for the years 1892 to 1901, shows that of 8430 persons bitten by rabid dogs, 77, or 0.91 per cent., died, whereas of 193 bitten by rabid wolves, 32, or 16.58 per cent., succumbed to rabies. The herbivora are apt to cause contusions with their blunt teeth, rather than punctured or lacerated wounds. Farmers are not infrequently exposed to infection from cattle through attempts to drench them, or from putting the hand in the throat in cases of "dumb" rabies, to remove a supposed obstruction.

Bites on exposed parts of the body are more dangerous than those made through clothing, since the latter retains the virus, and the comparatively clean tooth enters the body. For the same reason long-haired dogs when bitten escape infection more often than short-haired ones.

Bites in parts of the body having a rich nerve supply, as the face and hands, are particularly dangerous. In the former case especially, the virus is rapidly conveyed to the medulla. The same is true of bites in or about the large nerve trunks of the extremities.

The comparative danger is well shown in the statistics of 18,645 treated at the Pasteur Institute in Paris, as reported by Pottevin.

Location of bite.	Number treated.	Deaths.	Per cent.
Head	1,608	21	1.36
Hands	10,254	49	0.47
Limbs	6,783	20	0.29

Interesting figures on the same point are given from the Pasteur Institute at Kharkoff for the years 1892 to 1901.

Location of bite.	Number treated.	Deaths.	Per cent.
Upper extremities	5301	34	0.64
Lower extremities	2601	2	0.08
Head and face	946	73	7.72
Body	542	0	0

Rabies may be transmitted by the deposit of saliva containing the virus on abraded surfaces, as by licking. It may also be contracted

through wounds received in making autopsies on animals or persons who have succumbed to the disease. In all cases a solution of continuity is necessary for the absorption of the virus; it cannot pass through the healthy skin. It is doubtful if the virus can be absorbed through the digestive tract.

Not every person bitten by a rabid dog becomes infected. Leblanc gives 16.6 per cent. as the proportion, an estimate generally accepted as conservative and correct. Some series show much higher figures. Bouley reports 152 deaths among 266 persons bitten, but of these, 120 were bitten on the face and hands.

Sex.—Men are not only more liable to be bitten by rabid animals, owing to their various callings, but when bitten are more apt to contract hydrophobia. This is doubtless due to the greater protection afforded by the skirts, and not to any inherent immunity in women.

Age.—Two-fifths of all cases occur in children under fifteen years of age, according to Bollinger. Children are particularly liable to bites, owing to their habit of collecting together for play in the streets, their inability to recognize danger, and their lack of defence. For obvious reasons they are often bitten about the face. On the other hand, they appear to enjoy considerable relative immunity. Brouardel says that of every 100 persons below twenty years of age bitten, 31 die, while above this age, 62 of every 100 die.

Influence of Season.—The statistics of the Pasteur Institute, Paris, show that the largest number of patients apply for treatment in March, April, and May; the smallest in September, October, and November. A table compiled by D. E. Salmon, including 14,066 cases of canine rabies, gives the following results by months: January, 943; February, 1045; March, 960; April, 1323; May, 1419; June, 1467; July, 1435; August, 1294; September, 1145; October, 965; November, 933; December, 1137. More cases occur from April to September, inclusive, than during the rest of the year, due, no doubt, to the fact that dogs are more apt to run abroad during the warm season. Season and temperature have no real influence on the prevalence of the disease.

Virus.—Distribution.—The virus is always contained in the saliva, and appears to be excreted chiefly by the parotid gland, though not entirely so. The salivary glands themselves are virulent, though not so constantly as the mixed saliva. The saliva of the dog has been shown by Nocard and Roux to be always virulent twenty-four to forty-eight hours before the animal shows any symptoms of illness. The lachrymal glands, the pancreas and suprarenal capsules may contain the virus. It is also excreted in the milk at times. The blood and lymph are very rarely virulent, and Helman has shown that the virus is absent from the lymph glands in relation to the point of inoculation. The muscles and organs are innocuous.

Every part of the central nervous system constantly contains the virus, but it is especially concentrated in the medulla. The large nerve trunks are usually virulent, as is also the cerebrospinal fluid. Pasteur showed that the "entire nervous system, from centre to periphery, is capable of cultivating the virus."

Nature.—The exact nature of the virus is unknown. The behavior of the disease makes us certain that it is caused by a specific microorganism, which, after introduction into the body, undergoes a period of incubation, during which it multiplies and produces a toxin having a special action on the central nervous system, as in tetanus, to which it bears a striking analogy. Nocard in 1880, and Paul Bert in 1882, showed that, on filtration through plaster, the virus was held on the filter, the filtrate being devoid of pathogenic power. The virus will frequently pass a coarser filter, such as the Berkefeld V, and will sometimes penetrate a Chamberland F, under pressure. Several observers have found that the filtrate frequently produces cachectic and paralytic phenomena not unlike rabies in dogs and rabbits, but after death the medulla of the animal is incapable of injuring other animals, showing that the condition is a toxic one. In this respect also the analogy to tetanus is close, and the disease has been considered a toxoneurosis. Serial passages through susceptible animals increase the power of the virus, while it is attenuated by drying, heat, light, etc., as many bacteria are.

Innumerable attempts have been made to discover the causative agent, and, from time to time, observers have announced the finding of cocci, bacilli, yeasts, and protozoa, which they believed to be the pathogenic organism. None of these discoveries has stood the test of rigid investigation. The latest claim comes from the Pasteur Institute, Paris, where Manouelian and Viala[1] have described certain bodies from 1 to 2μ in size, found throughout the cerebrospinal axis, in the sympathetic system, in the peripheral nerves, and in the salivary glands, which they believe to be the parasite of rabies. Their work awaits confirmation. At present, the belief is held that the cause is a parasitic protozoan discovered by Negri and generally known as the "Negri body." This was the opinion of Negri from the first. His discovery has been amply confirmed, and most observers agree with his interpretation of the nature of the bodies as well as their significance. Negri traced a developmental cycle for the parasite, and classified it with the sporozoa. Williams and Lowden[2] also worked out a developmental cycle for the organism, placing it in the class protozoa. Williams named it *Neurorrhyctes hydrophobiæ*. Calkins does not consider the life history as given by Williams and Lowden as entirely established. He believes, however, that the organism is a protozoan but is not willing to accept the subclassification sporozoa.

A small minority oppose these views. Babes regards the Negri bodies as specific reaction products, indicating resistance on the part of the cell to the invading parasite, which may be demonstrated by special staining as granules in the interior of the bodies. The Negri bodies are therefore encapsulated parasites undergoing involution or degeneration. By others they are regarded as cell degenerations or inclusions. The constant presence of the bodies in rabies, and their absence from the brain in other diseases and in health is admitted universally.

[1] *Compt. Rend. de l'Acad. des Sciences*, Paris, January, 1924, No. 178.
[2] *Journal of Infectious Diseases*, 1906, vol. 3.

Resistance.—The virus is destroyed by heat, drying, and light. In dry air, protected from the light and from putrefaction, the spinal cords of rabbits lose their virulence gradually in fourteen to fifteen days, a fact made use of by Pasteur in preparing his vaccines. When in thin layers, the virus is entirely destroyed by drying in four to five days. Direct sunlight destroys it in about forty hours. In water the virus retains its power for twenty to forty days, or longer. Neutral glycerin preserves it unchanged for a long time. Roux found that after four weeks in glycerin at 30° C. the virus was unchanged in pathogenic power.

Galtier has found the virus active in the central nervous system of rabbits buried for twenty-three days, of sheep buried thirty-one days, and of dogs buried forty-four days. It is not injured by cold, resisting the prolonged application of a temperature 10° C. to 20° C. below zero. It is destroyed by 50° C. in one hour, or 60° C. in a half hour.

Investigators differ as to the effects of antiseptics. The best appear to be corrosive sublimate, 1 to 1000, citric acid in 6 per cent. solution, and saturated watery solution of iodine. The virulence of fixed virus is destroyed in eight minutes by 1 part of a 5 per cent. solution of formalin to 3 parts of virus. Mixed in equal parts it is destroyed in five minutes. Bile rapidly destroys the activity of the virus. When an emulsion of the bulb from a rabid animal is mixed with an equal volume of bile from a healthy or rabid rabbit, and allowed to stand a few minutes, it may then be inoculated without danger of causing rabies.

Penetration.—From the point of inoculation the virus makes its way to the central nervous system along the nerve trunks, producing no symptoms until the central system has been the seat of the virus for some time. If the spinal cord of an animal is cut, and a virulent inoculation then made in the hind extremity, it will be found, after a suitable period of incubation, that the spinal cord below the point of section is virulent, while above, it contains no virus. When the inoculation is made into the brain or upper extremity, the descent of the virus can be prevented by section of the cord. Roux showed that in rabies developing slowly after inoculation of the limb on one side, the virus may also be found in the peripheral nerves of the opposite side; if, however, the period of incubation is short, only the nerves on the wounded side contain the virus. Clinically it has been observed that the paralytic and convulsive phenomena are more marked on the side of the inoculation. Experimentally in small animals the circulation and lymph channels appear to play some part in the absorption of the virus.

Pathology.—There are no characteristic gross pathological changes. In man, congestion of the lungs and emphysema are common, due to the convulsive seizures. The muscles of the chest and pleuræ are sometimes ruptured in the same way. Congestion of the fauces, œsophagus, stomach, and larynx is commonly found. Of the internal organs, the kidneys, spleen, brain, and spinal cord show congestion.

Pathology; Histology.—Many authors have described lesions of the nervous system which have been thought more or less characteristic. Babes described what he considers the essential lesion—an accumulation of embryonic cells in the neighborhood of the central canal, and especially

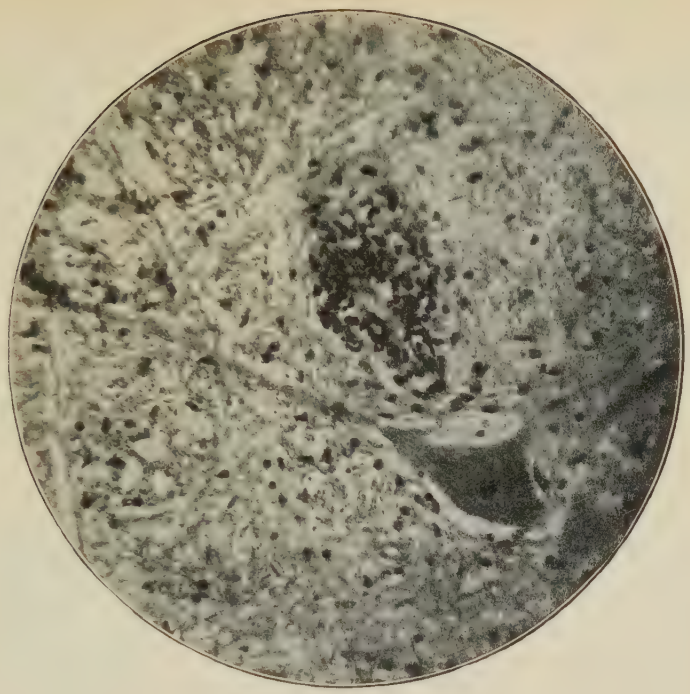
about the large modified cells of the motor centres of the bulb and cord. In the bulb he describes the pericellular accumulations of embryonal cells found by Kolessnikoff, for which he proposes the name "rabic tubercle." The cells of the bulbar nuclei undergo degeneration and show the various stages of chromatolysis. There is loss of the prolongations and progressive modification with even total disappearance of the nuclei, a dilatation of the pericellular space, and an invasion not only of this space, but also of the nerve cells by embryonal cells; at the same time, there appear small corpuscles which are hyaline, brownish, and in parts metachromatic. Many of the nerve cells become surrounded by a large zone of embryonal cells, degeneration of the cell follows, and when complete the embryonal cells occupy the cell area entirely, forming the "rabic tubercle."

In 1900 Van Gehuchten and Nélis discovered what they believed to be a diagnostic lesion. While recognizing and confirming many of the lesions described by other writers, they consider them secondary and of little importance. They believe that the virus acts by preference on the peripheral cerebrospinal and sympathetic ganglia. The lesions consist of atrophy, invasion, and destruction of the nerve cells by new-formed cells, due to the proliferation of the cells of the endothelial capsule. The new-formed cells increase in number, invade the protoplasm of the nerve cell, and finally occupy the entire capsule, the nerve cell proper having completely disappeared, while in its place is seen a mass of round cells. In advanced cases practically all the nerve cells may be destroyed, and the section has much the appearance of an alveolar sarcoma. These changes have been found in a great variety of animals.

In 1903 Negri announced the discovery of certain bodies in the nerve cells of rabid animals. They are found especially in the horn of Ammon. They are from 1 to 23μ in diameter, oval, round or triangular in shape, according to their size and position in the cell. They are strongly eosinophilic and consist of a fundamental substance, which is homogeneous and hyaline in appearance. Within them are clear areas which appear to be vacuoles in many of which granules may be found. There is usually a large central body surrounded by smaller ones. Aster-like forms are often seen. These inner bodies vary considerably in size, structure, and staining reaction, but are usually basophilic. The bodies vary greatly in size and number in different cases, and seem to be affected by the species of animal. In cattle they are usually numerous and large. Budding forms are frequently observed. They are especially numerous and large in cases of long incubation period (Negri). They are generally most numerous in the large nerve cells of the horn of Ammon, fewer in the cerebral cortex, the cerebellum, the medulla, and least of all in the spinal ganglia and vagus. They are quite resistant to external agencies, remaining unchanged for some days by putrefaction and one hundred and eighty-three days by desiccation. Material may be preserved in glycerin for eighty days without altering the Negri bodies. They are destroyed by a 33 per cent. solution of caustic potash.

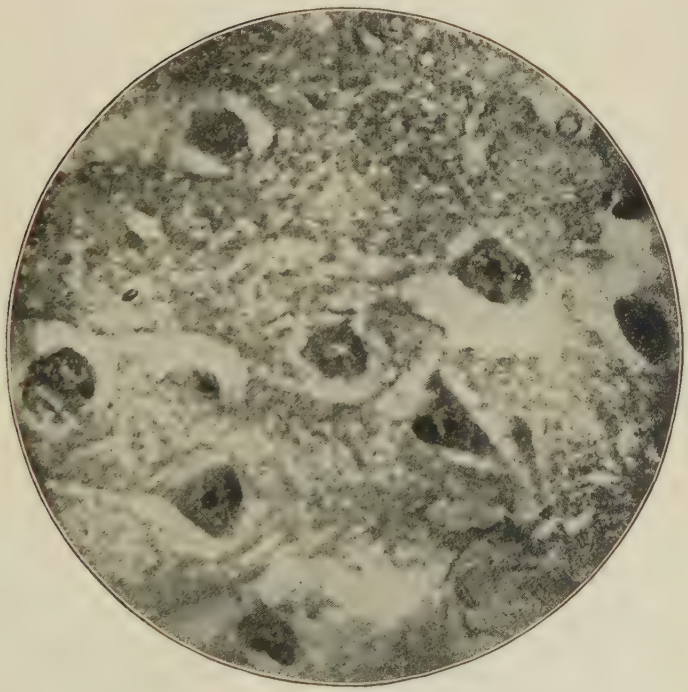
Postmortem Diagnosis.—There are no gross lesions which enable one to state positively that death has been due to rabies. In dogs, perhaps

Fig. 23



Rabic tubercle from medulla.

Fig. 24



Negri bodies in pyramidal cells of hippocampus.

the most constant feature is the absence of food from the stomach and the presence of foreign matter, such as straw, wood, hair, etc. Emaciation is usually marked and putrefaction takes place rapidly.

Formerly we were obliged to resort to inoculation of animals for a positive diagnosis. Rabbits are usually selected, and the inoculation made under the dura, since infection is more rapid and certain than when the inoculation is made elsewhere. Symptoms appear from the sixteenth to the twenty-first day, as a rule, but may be delayed for sixty days. The type of rabies following inoculation is usually the paralytic, though rarely the furious type is seen. The virus of rabies is concentrated in the medulla, and especially in the floor of the fourth ventricle. For inoculation the tissue is by preference taken from this area.

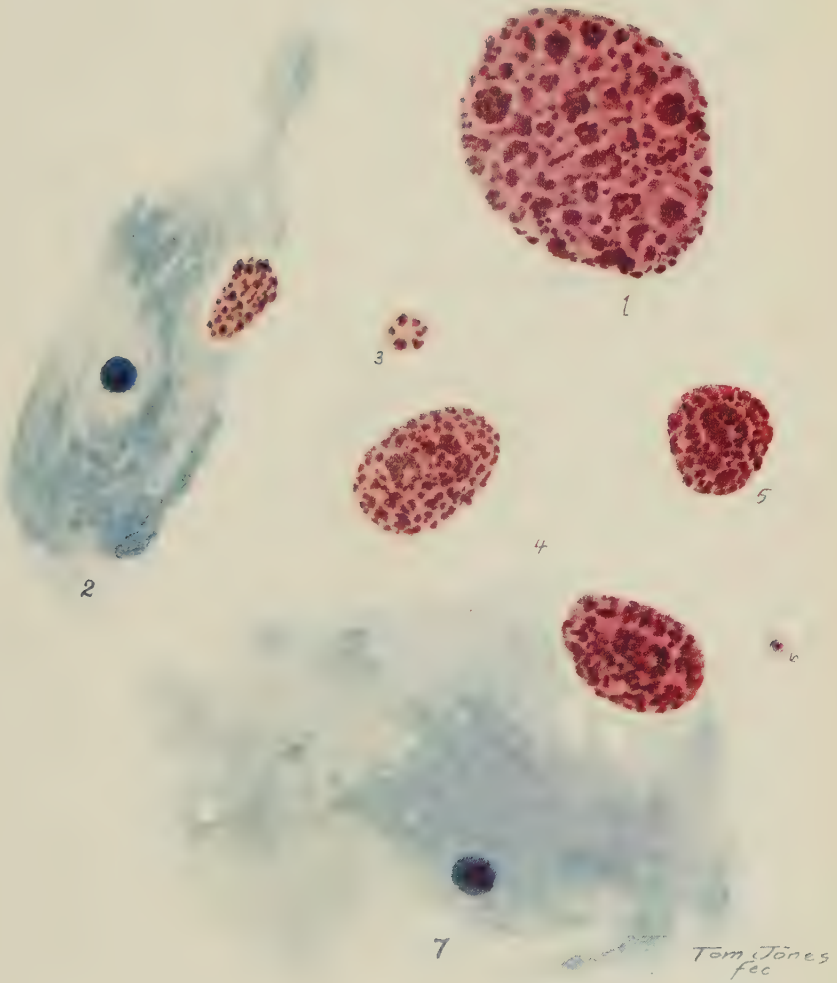
Microscopic Diagnosis.—On account of the time required, the inoculation of animals is of no service in determining the necessity of antirabic inoculations. Fortunately it is now possible to make a rapid diagnosis by microscopic methods. For diagnosis by the method of Van Gehuchten and Nélis, the plexiform ganglion of the pneumogastric nerve is selected, as it is easily dissected out, and presents the characteristic changes in the ganglion cells. In dogs, the ganglion is readily found by cutting down on the pneumogastric nerve in the neck, and following it up. Near the skull it divides into two branches, on one of which, the smaller, is found a small, oval, reddish ganglion, the cervical. The larger branch enters the plexiform ganglion, which is easily recognized by its fusiform shape, and white or grayish color. It is seldom more than a half inch from the foramen, and it is generally necessary to cut the nerve as it emerges from the skull. The ganglion may be prepared for section by any of the rapid methods.

The best stain for general use is hemalum (Grubler), made up with a 0.5 per cent. solution of carbolic acid, and counter-stained with eosin. While the lesions cannot be considered specific, since similar changes have been noted occasionally in other toxic conditions, and in the ganglia of aged dogs, yet by their extent and constant occurrence in rabies they have an unquestionable significance, and, in connection with even a meagre history, have an absolute diagnostic value. Certain precautions must be observed: The animal must be allowed to die of the disease. The lesions may be slight or entirely wanting in animals killed prematurely, and in such cases their absence does not preclude the existence of rabies. If absent after death from the disease, we can positively deny the existence of rabies.

A diagnosis can be made within six hours by rapid fixation and mounting, and is easily made within twenty-four hours.

The diagnosis by the *method of Negri* has advantages over the above in that the Negri bodies are usually found early in the disease, are not affected by putrefactive changes incident to delay in obtaining the material, and the technique is more simple. A small portion of the brain should be taken from the cortex of the cerebellum, and also from Ammon's horn, as the bodies may be numerous in one area and not in the other. The pieces of tissue may be fixed in Zenker's fluid, embedded in paraffin, and stained with eosin and methylene blue. The bodies show red against

PLATE I



Negri Bodies from Horn of Ammon of Dog.

Stained by Harris' method. (Jour. Infect. Dis., 1908, v.)

the blue background of the cell. The stains of Mann and Romanowsky are especially recommended.

A method for sections which is rapid and excellent has been devised by Andriani.[1] (1) Blocks of the hippocampus 3 mm. thick are fixed in acetone for two hours, then passed through xylol a half hour, xylol and paraffin a half hour, paraffin one hour. (2) Section and stain five minutes in: Malachite green, 20 centigrams; orange G., 2 grams; alcohol 90 per cent., 10 cc.; distilled water, 105 cc. (3) Remove – do not wash – and immerse from two to three minutes in: Chromic acid, 50 centigrams; potash alum, 1 centigram; distilled water, 100 cc. (4) Wash in water twenty seconds. (5) Pass through absolute alcohol, in which the excess of green passes out and a rose shade is produced; wash in xylol and mount in balsam. The Negri bodies are green, clearly defined against the nerve tissue which is orange.

An immediate diagnosis may generally be made by the smear method of Williams. Minute portions of brain substance are taken from the cerebral cortex about the crucial sulcus, the cortex of the cerebellum, and the hippocampus major. Crush these between two well-cleaned slides, and make a smear by drawing them apart lengthwise under gentle pressure so as to produce an even and fairly thin film. Dry in the air and fix in methyl alcohol for three to five minutes or in Zenker's fluid for fifteen minutes. Many methods of staining are in use. Among the best are Giemsa's solution, the eosin-methylene blue of Mallory, the rosaniline-methylene blue of Van Giesen, especially as modified by Moon, and the eosin-methylene blue method of Harris (Plate I).[2, 3] This last gives especially beautiful pictures, and is carried out as follows: (1) Fix smear in methyl alcohol one minute. (2) Wash in water to remove alcohol. (3) Immerse in old saturated solution of eosin in 95 per cent. alcohol one to three minutes (solution must be at least two months old.) (4) Wash two or three seconds in water to remove excess of eosin. (5) Immerse in fresh solution Unna's alkaline methylene blue five to fifteen seconds. (6) Wash briefly in water. (7) Decolorize in 95 per cent. alcohol, blot, and dry in air. The entire process requires less than five minutes.

Williams' modification of Van Giesen's stain, or some modification of it, is more widely used in this country than any other. It is made by mixing: Saturated alcoholic solution of fuchsin 0.5 cc.; saturated alcoholic solution of methylene blue 10 cc.; distilled water 30 cc. The smear is partly air-dried and fixed for ten seconds in neutral methyl alcohol to which 0.1 per cent. of picric acid has been added. It is then covered with the stain, heated until it steams, washed in tap water and dried with fine filter paper. The Negri bodies are magenta, the nerve cells blue, and the red blood cells yellow or salmon color.

The discovery of Negri has been abundantly confirmed in every part of the world. While there is still some doubt as to the exact nature of

[1] *Ann. de l'Inst. Pasteur*, 1924, **38**, 520.

[2] *Journal of Infectious Diseases*, 1908, vol. **5**.

[3] Since the World War, attempts to obtain an eosin which will give this stain have so far failed.

the bodies, it is certain at least that they bear a close relation to the causative parasite. They are found only in rabies, and their presence gives a positive diagnosis. Bertarelli states that in more than 1000 examinations Negri bodies were never found in animals free from rabies, and were present in all infected animals, with 3 exceptions. Williams quotes Luzzani as saying that of 457,297 cases of rabies as proved by the biological test only 9 failed to show Negri bodies in sections.

Incubation.—The average period in man is about *fifty* days, but it varies between wide limits. The great majority of cases occur between the twentieth and ninetieth day. Cases have been reported as developing several years after infection but are generally discredited. Gowers says, "It is, however, certain that the disease may occur after an interval of a year or eighteen months, and it is difficult, therefore, to deny the possibility of a longer interval." The shortest period of incubation is about twelve days. The development of rabies is not common after three months, and is quite rare after six months. The period of incubation is influenced by the location and severity of the injury, and apparently by the species of animal inflicting the bite. It is apt to be shorter when the bite is about the face or neck, or into large nerve trunks. Women show a shorter period than men, and children shorter than adults. Bites by wolves give shorter incubation than dogs, though this may be due to the greater severity of the attack and the location of the injury, which is usually about the head.

Symptoms.—As a rule, there are no symptoms during the period of incubation. The wound generally heals as any other similar injury without local thickening or glandular involvement. In some cases mental depression is marked, but it is usually due to anxiety and apprehension rather than to the disease. Instances have been reported by most reliable observers in which mental symptoms were noted in children too young to be apprehensive of danger, and in persons who were not aware that they had been bitten by a rabid dog. Three stages are usually recognized, but are not always well defined. The symptoms of the later stages are frequently prominent from the first.

1. **Premonitory Stage.**—This is often marked by irritation, tingling, or a feeling of numbness at the seat of the bite, or quite severe pain, lancinating in character, and radiating up the limb. These sensations may exist for as long as a week before other symptoms appear, although usually this stage lasts only twenty-four to forty-eight hours. The patient complains of general malaise, depression and melancholy, with extreme anxiety and a sense of impending danger. The sleep is disturbed; often there is great restlessness and irritability.

About this time symptoms referable to the throat appear, such as slight difficulty in swallowing liquids, or a slight choking sensation. The voice becomes husky, often there is precordial distress, with a sense of oppression, the patient frequently taking deep inspirations. Slight fever with increase of pulse-rate is commonly present; occasional rigors occur. During the early stages many patients show symptoms much like those characteristic of rabies in the dog: An unnatural suspicion, irritability of temper, surliness, desire to be alone, alternating with periods

of mental excitement and loquacity. Delusions and maniacal delirium appear as late symptoms.

2. **Stage of Excitement.**—The symptoms all increase rapidly in severity. The face takes on an expression of terror with marked pallor; the muscles are drawn and restless; the eyes have a "hunted look." There is intense thirst, but every attempt to swallow water brings on a spasm of the muscles of deglutition and respiration—the typical *hydrophobic spasm*. The extreme thirst impels the patient to make strong efforts to drink. The water is taken into the mouth, but as soon as it touches the fauces, it is expelled with considerable force, and violent spasmodic contractions of the muscles of deglutition and respiration come on. These attacks are accompanied by a sense of extreme dyspnœa, "even when the glottis is widely opened or tracheotomy has been performed." They increase both in intensity and frequency, and a cutaneous hyperesthesia develops, in consequence of which the slightest draught of air or contact with anything cold, is sufficient to determine an attack. The suffering of the patient, both physical and mental, is intense during the spasms, and the dread of them produces a mental condition which increases the ease with which they are excited. The hypersensitiveness may be so marked that the sight or sound of water, or even the mention of it, a strong light, or the reflection from a polished surface or looking-glass, brings on a spasm. To this result from the attempt to swallow water is due the name "hydrophobia." In man these spasms constitute the most distressing feature of the disease and the most diagnostic symptom.

With the advance of the disease, the convulsive attacks, at first confined to the muscles of deglutition and respiration, involve other groups of muscles and become general. They may be tetanoid with marked opisthotonos and suspension of respiration, or be "coördinated and closely resemble hysteroid convulsions." Not only is the frequency and intensity of the seizures increased, but the length of the paroxysms often becomes greater and death from asphyxia may occur. The skin and patellar reflexes are usually increased. Much distress is frequently caused by auditory and olfactory hyperesthesia. Slight odors precipitate attacks of sneezing and even convulsions.

The mucous surfaces are covered with thick tenacious mucus; the saliva is abundant and viscid, while inability to swallow it is often present. There are constant attempts to expel it, which are only partially successful, so that it hangs from the patient's mouth. Vomiting is frequent, the fluid being greenish-brown and sometimes containing blood.

The horror of the convulsive attacks is so great that delusions or maniacal delirium often appear. The delirium is most marked during the paroxysms; the patient may throw himself from the bed, and inflict severe wounds on himself without apparent pain. He may attempt to bite his attendants or spit at them. The delirium is not constant. During the intervals the patient can be brought to consciousness. He often shows anxiety for the safety of those about him, begging to be restrained from injuring them. The duration of this stage is from one and a half to three days.

3. **Paralytic Stage.**—The convulsive attacks, with the attendant mental symptoms, usually abate a short time before death, a paralytic condition taking their place, and the patient sinks rapidly, dying from exhaustion. Coma may precede death.

Temperature.—Babes lays stress on an elevation of temperature during the period of incubation. This has often been observed in animals, but its constant occurrence in man is not proved. In the early stages, fever is lacking or moderate, and throughout the disease may not exceed 100° or 101° F. Usually the temperature rises as the symptoms increase, reaching 103° to 105° F., or even more, just before death.

The urine frequently contains albumin, sometimes sugar and blood.

The pulse is quick throughout. During the last stages it becomes more rapid, small in volume, and irregular. Increased sexual desire is not infrequent in the early stages and may increase as the disease advances. Persistent priapism may add to the difficulty of urination.

Paralytic Rabies.—Sometimes the convulsive attacks, the excitement and delirium, and the hydrophobic spasms are entirely lacking, and we have typical *paralytic rabies*, so often seen in dogs and in animals inoculated experimentally. This type is especially apt to follow extensive bites when the amount of virus is large. According to di Vestea and Zagari, it is apt to follow bites about the lower extremities, while the furious type is usually the result of bites about the head and hands. The first symptoms are usually in the bitten limb, but sometimes violent pains extend from the lower trunk down the limbs, which feel heavy and difficult to move. Paraplegia soon comes on, and may be the first symptom. The course of the disease is an acute ascending paralysis, involving the sphincters and the muscles of the trunk, and ending in death by paralysis of the muscles of respiration or by cardiac syncope. Diagnosis may be impossible except by inoculation of animals, and microscopic examination after death.

Duration.—Death usually occurs between the second and fifth days; rarely the patient may survive eight or nine days. Bouley found that of 90 cases, 74 died during the first four days—most of them on the second and third days. In 16 cases life was prolonged beyond the fourth day. In the paralytic type death often does not take place until the seventh day.

Rabies of the Dog.—The disease is seen in two types, a furious, and a tranquil or paralytic type.

Furious Type.—In the furious type the first symptoms consist solely in changes in disposition, manifested by distress or uneasiness, and restlessness. The animal is easily excited. At this stage, he does not usually show a disposition to bite; he is docile and obeys orders, though not so quickly as in health; he soon seeks solitude and shows a disposition to hide in dark corners, or burrow in the straw of his kennel; periods of calmness alternating with marked excitement are observed; he still shows affection for his master but may be irritated by strangers, or, being surprised by touch or blow, may inflict a bite. The appetite is still good and may be excessive. Soon the restlessness becomes more marked; the dog is constantly in motion; he is apt to tear carpets, rugs,

etc.; he shows signs of delirium, looking off into space apparently seeing some imaginary object; at times he will attack an imaginary enemy. He will still respond to his master's voice, but his attention cannot be held for any length of time. At this early stage, the voice becomes modified, which is one of the most typical symptoms. Instead of the natural bark, the latter part of the note becomes prolonged and of a higher pitch, going off into a plaintive cry, and in succeeding short barks which may follow, the jaws do not close completely.

This symptom may be lacking at times and certain dogs remain quiet. The appetite diminishes about this time; food is taken with more or less difficulty, and soon it is refused, swallowing having become painful and difficult. The animal may appear to have a bone stuck in its throat, which often tempts the owner to make an examination for some obstruction. There is no fear of water, and the animal drinks water and other liquids quite greedily, until paralysis of the constrictor muscles of the pharynx makes swallowing impossible.

The excitement becomes marked and the animal is now furious. If an object is presented to him, he seizes it with power, and attacks the bars of his cage. If at liberty, he attacks everything in his way, swallowing all sorts of articles, such as wood, paper, straw, and stones. At this time he wanders, running with mouth open; the eyes have a wild look; he attacks every object or animal which comes in his path. As a rule, he runs straight ahead and does not turn out of his way to attack animals. The dog may travel tremendous distances, but is apt to return to his home, exhausted and covered with dust and blood; or he may continue until he falls exhausted, as many as fifty miles being covered. Very soon paralysis sets in, commencing in the hind legs, and finally becomes general. The dog is no longer able to stand; weakness becomes more marked and stupor sets in, which becomes deeper and ends in death. The course is rapid, covering from six to ten days, and averaging from four to five days. The symptoms are so characteristic that they can scarcely be mistaken for any other disease. The furious type is the most common.

Paralytic Type.—The paralytic type, ordinarily spoken of as "dumb rabies" constitutes from 15 to 20 per cent. of all cases. In certain countries, as in Turkey, it is the prevailing type, which explains the relative rarity of rabies in man in this country where dogs abound. The onset is the same as in the furious type, but the excesses of fury are lacking. For several days the dog appears restless, seeking seclusion and dark places. The paralysis may commence in various parts of the body, but, as a rule, affects first the muscles of the jaw, which soon drops, the dog being unable to close its mouth, and the tongue hanging out; the whole expression of the animal is pitiful; an abundance of saliva runs from the mouth; the taking of water is impossible; the mouth becomes dry, covered with dust, and brownish in color. The animal is quiet; he does not respond to provocation, nor does he seem to wish to bite. The progress is more rapid than in the furious type. The paralysis extends, and death occurs on the second or third day.

In the "dumb" type it is common to suspect an obstruction in the

throat, and in the attempt to locate it the saliva may infect wounds of the hand. The animal never wanders and, being unable to bite, the danger of transmission is slight.

Diagnosis.—Hydrophobia may be confounded with tetanus, hysteria, acute mania, and lyssophobia.

From *tetanus* it is distinguished by the longer period of incubation, the absence of trismus and the "risus sardonicus," and the complete absence of spasm during the intervals. The mental condition is different; the anxiety and the restless irritability of hydrophobia are lacking in tetanus. The most characteristic symptom of hydrophobia is the respiratory spasm excited by attempts to swallow water. *Hysteria* sometimes simulates hydrophobia closely, especially in cases in which the patient has been bitten by a dog and has been anxious about it. In these instances there may be general convulsions with constant barking and biting. A careful review of the history and symptoms, and especially the absence of the respiratory spasm, usually make the diagnosis clear. The differentiation from *mania* may be difficult at first, and must depend largely on the history. The rapid course will soon clear up the diagnosis. As Gowers says, "No patient ever passed from mental health to a state of imminent danger in two or three days in consequence of simple insanity."

Lyssophobia is the name given to symptoms sometimes seen in nervous persons who have an exaggerated fear of hydrophobia. Autosuggestion determines spasms in the throat on swallowing, and a dread of water may follow in consequence. The symptoms usually occur soon after the bite, sooner in fact than the shortest period of incubation in the true disease. There is lacking also the true respiratory spasm, and the patient can usually be quieted. It has not been proved that death ever takes place from lyssophobia.

Prognosis.—Reported instances of recovery at best are so rare that a fatal outcome must always be looked for. In dogs and some other domestic animals spontaneous recovery has been observed both after inoculation and natural infection.

The prognosis as regards bites by rabid animals depends on the animal inflicting the bites, the size, number, character, and location of the wounds; also on the length of time between the injury and cauterization, and on the thoroughness with which it is done. When done properly and thoroughly the protection is very great—in moderate wounds practically absolute. The statistics of Proust show that, in a series of 117 cases, not cauterized, there were 96 deaths; while among 249 cases, in which cauterization was practised, only 89 deaths occurred. When the wounds are multiple and lacerated, and especially when about the face and head, thorough cauterization is difficult or impossible.

The outlook is most favorably influenced by the Pasteur treatment At the parent Institute, 1886-1923 inclusive, 45,298 cases have been treated with 150 deaths, a mortality of 0.33 per cent. Since 1910 there have been six years in which no death occurred.

Statistics collected by Högvès, including 54,620 persons treated at 24 institutes, show that the total mortality was only 0.77 per cent. In

Hungary, where rabies is very prevalent, from 1890 to 1895, there were 5899 persons bitten, of whom 4914 received the Pasteur treatment, with a mortality of 1.2 per cent., while among those not treated 14.94 per cent. died of rabies.

As in other methods of vaccination, immunity is produced only after a certain time, and in cases of short incubation, or of late commencement of the treatment, the disease may manifest itself before the vaccinal effect has been procured. For this reason certain cases of death are justly excluded from the statistics of the Pasteur treatment. Their admission would, however, raise the percentage very little. The work of Krauss and Kreissl throws much light on the production of immunity by the Pasteur treatment, and emphasizes the importance of beginning treatment promptly. These authors find that the serum of healthy men, as a rule, does not contain any protective property against the virus of rabies, nor is any found immediately after the completion of vaccination, but twenty-two days later marked antirabic power is present, and is retained for a long time. Cases in which the treatment is unsuccessful are probably due to the absence of this property. It is important that the treatment be begun within one week of the bite.

Treatment.—When the disease has declared itself, this is purely palliative, and directed to relieving so far as possible the suffering of the patient. Our efforts must be directed to preserving the strength, and lessening the frequency of the paroxysms. Every source of annoyance should be removed. The room must be darkened, warm, and quiet. Only the necessary attendants should have access to the patient. Especially must draughts of air and sharp noises be avoided. The diet should be as concentrated as possible, and liquid. Osler advised the use of cocaine to the fauces to facilitate the taking of liquids. If the dysphagia is marked, recourse must be had to rectal enemas. Thirst must be relieved by the same measures.

The list of recommended drugs is a long one but none has any specific value. Hypodermic injections of morphine and inhalations of chloroform will generally give more relief than any other drugs. They should be used from the beginning, and no time wasted with milder antispasmodics. Calabar bean and curare have been recommended. Three cases of cure are credited to curare, one of which Gowers considered "undoubtedly genuine." As it acts by paralyzing the motor nerves, artificial respiration may become necessary.

Forcible restraint during the paroxysms is often required. Tracheotomy has been advised, but is useless, since the dyspnœa is due to spasm of the respiratory muscles, and the glottis is not closed.

Preventive Treatment.—The bite of any suspicious animal should receive prompt attention. The invariable rule must be: Cauterize as soon as possible and in the meantime do everything to get the virus out of the wound and prevent its absorption. Open the wound freely so that every part of it is exposed. Encourage bleeding by cupping or suction with the lips, the mouth being well washed after each application. Bathe abundantly, preferably with tepid water. If the wound is on a limb, a ligature may be applied above the site. As soon as possible the

wound must be thoroughly cauterized. For this purpose fuming nitric acid is the best agent. It must be applied to every portion of the wound with a fearless hand, deep punctures having previously been laid open with the knife. In the absence of nitric acid, lunar caustic, the actual cautery, or strong antiseptics should be used. The importance of early and thorough cauterization cannot be overstated. There is strong experimental evidence that laying open the wound and the free use of nitric acid will save a certain proportion of cases even after a lapse of twenty-four hours. It should never be neglected, since it retards the development of the disease, and renders the Pasteur treatment more certain of effect.

Pasteur Method of Immunization.—Pasteur observed that by residence in the nervous system of certain species of animals the power of the virus was exalted, while, on the contrary, in other species it became attenuated. By inoculation of rabbits in series, one from the other, we obtain a virus of greatly increased virulence, so that after about one hundred passages they die with great regularity on the sixth or seventh day. Beyond this point no increase of virulence can be obtained, therefore Pasteur gave it the name "fixed virus" in order to distinguish it from that found in dogs under natural conditions, which is known as "street virus." On the other hand, when monkeys are inoculated in series, the period of incubation becomes gradually lengthened, until after a time the virus becomes so attenuated that it no longer causes death. With Chamberland and Roux the method in universal use was worked out, depending on the fact that the rabic virus contained in the spinal cords and brains of rabbits becomes attenuated fairly evenly and regularly by drying when protected from putrefaction, so that it is harmless at the end of fourteen or fifteen days. Rabbits are inoculated subdurally with the fixed virus daily. At death, the spinal cord is removed with strict aseptic precautions, cut into three pieces, and suspended in large bottles containing a layer of caustic potash. These bottles have an opening near the bottom as well as at the top, both of which are plugged with cotton, so as to allow free passage of air. They are kept in a dark room at a constant temperature of 23° C. Thus, a full series of cords from fourteen days up to one day old is at hand, giving various attenuations of the virus from the weakest to the strongest. The usual dose is a portion of cord 2 to 3 mm. in length, which is prepared for injection by trituration and suspension in normal salt solution or bouillon.

The original scheme of injections as devised by Pasteur has been greatly modified. Pasteur began with fixed virus which had been dried for fourteen days, and never gave a more virulent cord than one dried for three days. Experience has shown that fixed virus is greatly modified in its virulence for man, and that it is not necessary to begin with such extreme attenuations. In fact, Ferran, Proescher, and others use unmodified fixed virus in quite large doses. The dilution of fresh fixed virus devised by Högyès has gained in favor. It is used with excellent results in several states, and is prepared by certain reliable biological houses. Högyès believes that the attenuation of virulence obtained by Pasteur was a numerical diminution of the rabies organism which could be obtained

more accurately by simple dilution of fresh fixed virus with salt solution. Dilutions varying from 1 to 100 to 1 to 10,000 are prepared and injected subcutaneously, begining with the highest dilution and reaching the lowest on the fourteenth day in mild cases, or on the twentieth day in severe cases. Phillips[1] modified this method by giving 60 mgm. of dead fixed virus daily for three days, and has also devised a method of storing standardized fixed virus. He reports 1540 cases treated with 1 death. The Georgia State Laboratory, also using a modification of Högyès method, reports 2207 cases treated with no death, and no treatment paralysis.[2]

As practised today at the Pasteur Institute in Paris, the treatment is modified according to the urgency of the case. The following scheme of injections is followed at the Pasteur Institute in Paris.

Days.	Cord, days.
I. *Benign cases*	
1	5
2	5
3	4
4	4
5	3
6	3
7	4
8	3
9	2
10	4
11	3
12	2
13	3
14	3
15	2
II. *More Grave Cases*	
16	4
17	3
18	2
III. *Grave Cases*	
19	3
20	3
21	2
IV. *Very Grave Cases*	
22	3
23	3
24	2
25	2

Tests made at the Hygienic Laboratory, and elsewhere, show that there is not much, if any, difference in the protecting power of the various methods, provided a good strain of fixed virus is used. Those schemes of injection which utilize most the cords of higher virulence give the best results. In America, the scheme of the Public Health Service is largely followed, beginning with cords of the eighth day and proceeding rapidly to those of the third, second, and first day.

[1] *Jour. Immunol.*, 1922, **7**, No. 5.
[2] *Am. Jour. Public Health*, 1923, **13**, No. 9.

SCHEME FOR INTENSIVE TREATMENT.

Day.	Cord.	Amount.		
		Adult.	5 to 10 years.	1 to 5 years.
1	8–7–6	2.5 cc.	2.5 cc.	2.5 cc.
2	4–3	2.5 cc.	2.5 cc.	2.0 cc.
3	5–4	2.5 cc.	2.5 cc.	2.5 cc.
4	3	2.5 cc.	2.5 cc.	2.0 cc.
5	3	2.5 cc.	2.5 cc.	2.0 cc.
6	2	2.5 cc.	2.0 cc.	1.5 cc.
7	2	2.5 cc.	2.5 cc.	2.0 cc.
8	1	2.5 cc.	1.5 cc.	1.0 cc.
9	5	2.5 cc.	2.5 cc.	2.5 cc.
10	4	2.5 cc.	2.5 cc.	2.5 cc.
11	4	2.5 cc.	2.5 cc.	2.5 cc.
12	3	2.5 cc.	2.5 cc.	2.0 cc.
13	3	2.5 cc.	2.5 cc.	2.0 cc.
14	2	2.5 cc.	2.5 cc.	2.0 cc.
15	2	2.5 cc.	2.5 cc.	2.0 cc.
16	4	2.5 cc.	2.5 cc.	2.5 cc.
17	3	2.5 cc.	2.5 cc.	2.5 cc.
18	2	2.5 cc.	2.5 cc.	2.0 cc.
19	3	2.5 cc.	2.5 cc.	2.0 cc.
20	2	2.5 cc.	2.5 cc.	2.5 cc.
21	1	2.5 cc.	2.5 cc.	2.0 cc.

The Pasteur treatment should always be begun as soon after the bite as possible. It is useless after the symptoms have declared themselves. The probabilities of failure are least in those who present themselves for treatment during the first week, since only those in whom the period of incubation will be less than twenty days will fail to receive immunity. The usual incubation exceeds this time considerably. It has been abundantly shown experimentally, as well as by comparative mortality tables, that the period of incubation is lengthened in persons who succumb after partial or complete treatment.

Effect of Treatment.—*Treatment Paralysis.*—In the great majority of cases, no ill effects follow the injections, even when the person has not been infected. Untoward symptoms, varying from those of mild neuritis to those of acute ascending paralysis, ending in death, sometimes occur. In mild cases "flashes," numbness and more or less paralysis are seen. The symptoms may appear within a week of the first injection or be delayed until sometime after completion of the treatment. Adults are almost exclusively affected. Most patients recover spontaneously. The occurrence of treatment symptoms varies according to the method employed:

Method.	Number of cases treated.	Cases of paralysis.	Proportion.
Classical Pasteur	32,676	6	1:5448
Modified Pasteur	8,657	16	1:541
Högyès	51,417	3	1:17139

One hundred cases have followed 217,774 treatments. Of 188 cases, 29 were fatal. The treatment is not entirely devoid of danger, though it is slight, and not to be weighed against the good results.

The cause of paralysis is not understood. Roux, Koch and others believed that the symptoms were due to street virus the effect of which is so modified by the vaccine as to produce an abortive type of rabies. By others the fixed virus, or its contained toxin, is held responsible, and this seems to have been proved in certain cases. Harvey and McKendrick[1] regard the symptoms as anaphylactic phenomena. No one factor explains all cases.

Duration of Immunity.—We have no statistics for man. In dogs the protection has been found to have disappeared in 21 per cent. at the end of one year, in 33 per cent. after two years, while in others it has persisted for five years. Persons bitten a second time by a rabid dog should again receive treatment, unless a very short time has elapsed.

Serum Therapy.—Serums obtained from immunized animals have been used, but while the experimental results in the production of an antirabic serum are encouraging, its use has not gained headway.

Prevention.—Rabies is a preventable disease. Since more than 90 per cent. of all cases are due to bites from dogs, and since it is kept alive in the canine race, our measures must be directed to the control of those animals. It is better and more humane to have them under supervision than to subject them to the extreme measures sometimes enacted during the terror which reigns in a community in which an outbreak of rabies occurs. The wholesale destruction of dogs sometimes seen is cruel and wholly unnecessary. Among the measures proposed for the control of dogs may be mentioned high tax, muzzling, and the leash, with the destruction of homeless and wandering animals. The results of muzzling justify its recommendation, and there is little doubt that its strict enforcement will eradicate rabies from any community in a short time. Great Britain furnishes a striking example of its efficacy. In 1887 there were 217 cases of rabies in Great Britain; in 1888, 160; and in 1889, 312. The increase caused alarm and muzzling was enforced, as a result of which in 1890, 129 cases were seen; in 1891, 79 cases; in 1892, 38 cases. There was much opposition to muzzling and the ordinance was relaxed. In 1893 the number of cases rose to 93; in 1894, to 248; and in 1895, to 672. Muzzling was again enforced, resulting at once in a marked decrease of cases to 438 in 1896, 151 in 1897, 17 in 1898, 9 in 1899, and none in 1900.

More remarkable still are the results which have been obtained in the Department of the Seine. The repressive measures have consisted largely in the destruction of stray dogs and a dog tax. In 1887 there were 2770, and in 1901, 623 patients treated at the Pasteur Institute in Paris; in 1913 only 330. There has been no death from rabies in the Department of the Seine since 1904. These results are all the more striking when we remember the statement of Nocard that "the Department of the Seine was a focus of infection unique in the world." They furthermore effectually dispose of the often repeated claim of the antivivisectionists, that Pasteur Institutes spread hydrophobia.

Vaccination of dogs by the method of Pasteur has always been prac-

[1] *Theory and Practice of Antirabic Immunity, Calcutta,* 1902.

ticable, but the expense prevented its general use. The loss of dogs and livestock, the difficulty of controlling the disease by repressive measures and the increased use of vaccines in the control of various diseases have led to the development of a cheap and practical method of protecting dogs. The vaccine (Umeno and Doi[1]), is prepared by grinding the brain and cord of rabbits which have died from fixed virus with four times the volume of phenolized glycerin and water, the proportions being glycerin 60 parts, water 40 parts, phenol 1.25 per cent. A single injection under the skin is given. In Japan 31,307 dogs were vaccinated, with only 1 failure against natural exposure. In this country approximately 25,000 vaccinations have been done with no recorded failure.[2] Most biological houses manufacture the virus, and one state has required the immunization of dogs by this method. The immunity persists for one year.

[1] *Kitasato's Arch., Exp. Med.*, 1922, **4**, 2.
[2] *Jour. Am. Vet. Med. Assn.*, 1924, **66**; new series, 1924, **17**, 6.

CHAPTER VIII

RHEUMATIC FEVER

By FREDERICK J. POYNTON, M.D., F.R.C.P., (Lond.).

Etiology.—*Rheumatic fever* takes a very prominent position among the diseases of temperate climates, and has from ancient times attracted much attention. As a result of modern investigation the writer believes that it is an infective disease and that references to the older theories of its origin may be omitted. In doing this the writer fully recognizes that the earlier investigators provided valuable material for our present knowledge.

When we investigate the reasons for looking upon rheumatic fever as infective, we find convincing evidence. To quote the late Dr. Cheadle: "The occasional epidemic prevalence, the variability of type, the incidence upon the young, the occurrence of tonsillitis, of endocarditis, of pneumonia, of erythematous eruptions; the rapid anemia, the tendency to capillary hemorrhage and albuminuria; the implication of the joints, the relapses, the occasional supervention of hyperpyrexia, the nervous disturbance, the specific power of salicylic acid, are all suggestive of an infectious disease." The pathological and bacteriological facts in support of this view are also most convincing.

The exact nature of the infection has led to much controversy, and at present there is no general agreement upon this point. The morbid anatomy of rheumatic fever points to its classification among the diseases that result from micrococcal infections; that is to say, with diseases that result from infections with streptococci, staphylococci, and pneumococci. The several views are as follows: (1) That there is no specific microorganism, but the disease is a form of septicemia which owes its origin to staphylococcal or streptococcal infections. (2) That the disease is due to a specific bacillus. (3) That the microörganism is a diplococcus. (4) That the exciting cause is unknown.

The *first* view, that the disease is an attenuated pyemia, is widely held. Yet, in the writer's opinion, those who hold it have never established their position, and to it there are obvious and grave objections. In the first place rheumatic fever is a very common disease—far more common than the various forms of pyemia; yet it is most exceptional to find that it arises in connection with pyemia. There are puzzling cases which follow otitis media or a tonsillar abscess which to some extent support this view. Yet for one of these, hundreds of cases of rheumatic fever arise in such a way and run such a course that they cannot be grouped as examples of attenuated pyemia, without making an assumption not justified by facts. No value can be attached to the statement, commonly made, that rheumatism is a form of septicemia. Any infection, if sufficiently severe, will cause a septicemia, and such a vague statement gives no real assistance toward the proper understanding of the disease.

Again, rheumatic fever can be most deadly. What more terrible poisoning can be found than a severe attack with hyperpyrexia? This is certainly not an attenuated infection, and it certainly is not pyemia. Lastly, because various micrococci have been found and isolated from the tissues in rheumatic fever, this does not constitute a proof that they are a cause of the disease; or because various micrococci have produced arthritis and endocarditis in animals, this is no proof that they are therefore the cause of rheumatic fever. Many infections in man cause arthritis or endocarditis and yet the condition need not be rheumatic fever. The cardinal rules of investigation must be followed; a microörganism must be found with constancy in the important lesions of the disease; it must be isolated and cultivated outside the body; it must produce similar lesions in susceptible animals and must be again isolated from these lesions. No proof short of this suffices; and until this proof has been obtained for more than one micrococcus the view that various attenuated micrococci are causes of rheumatic fever is not established.

The *second* of these views, which looks upon the disease as the result of an infection with a specific bacillus, is not substantiated. A large bacillus was found by Achalme in 1891, and later other French observers, in particular Thiroloix and Rosenthal,[1] who stated that they have reproduced experimentally the rheumatic lesions.

The *third* view maintains that the cause is a diplococcus belonging to the group of streptococci allied to the *Streptococcus pyogenes* on the one hand and to the *Pneumococcus lanceolatus* on the other. This diplococcus has been isolated by a considerable number of investigators and its relationship to the disease worked out step by step. Triboulet and Apert in 1898 placed the position of this diplococcus upon a firmer basis by producing mitral disease in a rabbit by an injection of the microorganism obtained from the blood of a patient with rheumatic fever. Westphal, Wassermann, and Malkoff, in 1899, produced fever and multiple arthritis in 80 rabbits with a similar microörganism, obtained from a fatal case of rheumatism. Paine and the writer in 1900 published the results of an independent investigation in which they isolated this diplococcus from 8 successive cases of rheumatic fever and showed its presence in the most important human lesions; they produced these various lesions in rabbits and isolated the diplococcus from the animal tissues. Since that date they have increased the number of cases from 8 to 75 with only occasional failures.

The results of experiments are on the whole remarkably constant, and the reader cannot lose sight of the fact that a microörganism which is present in the lesions of rheumatic fever is capable of reproducing similar lesions in animals. Vernon-Shaw in 1903 demonstrated that monkeys were susceptible to the infection with a culture obtained by the writer from rheumatic pericarditis immediately after death. Fritz Meyer, Ainley Walker and Beatson, Beattie, Longcope and Lewis, Bracht, Wachter, Coombs, Miller and Kettle, Herry and Rosenow have confirmed many of the observations and have added more facts.

[1] *Gaz. d. hôp.*, October 19, 1907.

The chief characteristics of the microörganism are: It is a small micrococcus 0.5μ in diameter, and usually grows in pairs or in short chains. As a rule it does not show a capsule, but there is reason to believe that in the human tissues the appearance of capsulation may be occasionally found. It stains readily with aniline dyes. Some writers have stated that it retains Gram's stain; this is undoubtedly correct; but it does not retain this stain with great tenacity.

Degenerative forms are common, and the micrococcus then becomes swollen or pear-shaped. Some discussion has arisen over the name that should be given to it, but there seems no good reason for altering the name that Paine and the writer originally gave to it in 1901—the "Diplococcus rheumaticus," for it will be found in the majority of instances as a diplococcus rather than a streptococcus, and it is a cause of rheumatic fever. If a descriptive name is needed the "Diplococcus rheumaticus" is the most accurate—if a family name is required then "Streptococcus rheumaticus."

Cultural Characteristics.—*In bouillon* at 37° C. there is in twenty-four hours turbidity with slight flocculent deposit. In three days the fluid becomes clear and there is a distinct deposit. The medium becomes acid. *Gelatin (Stab):* In forty-eight hours minute colonies appear along the track of the needle; there is no liquefaction. *Blood agar:* This medium is one of the most favorable. Fresh blood is smeared upon the agar, and incubated for twenty-four hours. In twenty-four hours after inoculation minute white colonies are visible; these tend to remain discrete and alter the blood pigment to a rusty brown color. A noteworthy point is the remarkable vitality of the microörganism upon this medium, and the original culture isolated by Paine in 1899, grew for years in subculture. *Milk and bouillon* (equal parts) slightly acidified with lactic acid. This medium is a most serviceable one for isolation of the microorganism. In twenty-four hours the milk is coagulated. *Litmus milk* (blue) is turned a pinkish tint in forty-eight hours and the milk coagulated. Vernon-Shaw found that the best medium was glycerin, veal broth containing 2 per cent. peptone, and 1 per cent. alkaline to phenolphthalein. Beattie finds a definite and very distinctive reaction in the production of acid and precipitation of the bile salts in MacConkey's bile salt lactose broth.

A feature of this microörganism is the power it possesses of producing acid. Although a production of acid is a property common to many bacteria, this one possesses the power in a marked degree. Many workers have investigated these acids, and it is clear from their investigations that they vary with the medium in which the microörganism is grown. Walker and Ryffel directed attention to the large quantity of formic acid that the microörganism forms, and have extracted it from the bodies of the organisms themselves. Further investigations can alone show how much specific value we can attach to this formation of formic acid. In any case, however, it is a very interesting point that an acid which produces such an irritant effect upon the tissues should be formed in considerable quantity.

Although it is sometimes a difficult matter to demonstrate them,

the diplococci are probably present in all the chief rheumatic lesions. At one time or another they have been demonstrated in the endocardial and pericardial tissues, in the pleuræ, peritoneum, pia mater, synovial membranes, nodules, lungs, urine, and blood.

The writer has purposely avoided the use of the term "specific" as applied to the "Diplococcus rheumaticus;" and the present position of the etiology appears to him to be this: Rheumatic fever is a *specific disease*, and so far as our knowledge goes owns but one exciting cause, variously called a diplococcus, streptococcus, or micrococcus. The bacteriologist would wish, perhaps, to go further and say that this diplococcus is specific; such may prove to be the case, and is probable; but the discovery of a specific test for a microörganism is a different matter to establishing it as the cause of a specific disease.

An outstanding difficulty in the acceptance of this view of the causation is the failure of skilled bacteriologists to verify the presence of the diplococcus in the lesions, and to explain, if the disease is due to the streptococcus viridans (diplococcus rheumaticus), why antibodies against these organisms cannot be demonstrated in the serum of patients. No doubt general opinion favors the last view that the exciting cause of rheumatic fever is unknown. Libman in his recent papers writes definitely to this effect. On the other hand Carey Coombs in his recent monograph on rheumatic heart disease, as the result of entirely independent researches at Bristol writes thus: "Even now after several decades of research there is no general consensus of opinion though there is a slow but steady drift toward the view first expressed in 1900 by Poynton and Paine that the cause is to be found in a small strepto-diplococcus. He himself is prepared to go further and expresses the opinion that "It seems the time has come when the diplococcus rheumaticus should be accepted as the cause of human rheumatism."

The writer himself recognizes that after so many years of advocacy his own opinion, which is unchanged, can carry with it no added weight, but would point out that Dr. Nabarro, Director of Pathology at the Hospital for Sick Children, Great Ormond Street, has year after year isolated strepto-diplococci from cases of rheumatic fever and has at present eight different strains. The objection of agonal infection can be safely ruled out for the writer has seen too many examples from living cases which have moreover produced on experiment, carditis and arthritis.

The *fourth* view, which maintains that the exciting cause has yet to be demonstrated, still waits confirmation.

Secondary Factors.— *Heredity* is admitted as an important predisposing cause, and in a series of cases one is struck by the great frequency with which a family history of the disease is obtained after all allowance has been made for the vague use of the word "rheumatism." A distinction should be drawn between the "rheumatic diathesis" and those rare cases in which the mother suffered from rheumatic fever during pregnancy and the child is born with active carditis. In these cases there is probably a direct infection through the placental circulation.

The following analysis from the late Dr. Cheadle's private records illustrates the influence of heredity. In 32 consecutive cases, in 23 or

70 per cent. there was a definite history of rheumatic fever in near blood relations. If chorea and erythema are taken as sufficient evidence, the proportion was raised to 31 out of 33, or 93 per cent. If all the cases of arthritis, chorea, and morbus cordis were taken together, of 180 cases 103 gave a definite family history (58 per cent.).

Age.—Rheumatic fever is rare under five years of age, but from that time up to fifteen its frequency greatly increases; throughout adult life it is met with, but in advancing years the tendency diminishes considerably. It is an error to suppose that this disease occurs more frequently in adult life than in childhood.

Sex.—Allowing that the male adult is more exposed to sudden chills and severe exposure by his occupation, there is no striking difference except in childhood when the disease is more frequent in females owing to the far greater number of cases of chorea.

Climate, Season, and Locality.—The disease is ubiquitous, but is more frequent and severe in temperate and changeable climates. The majority of cases occur in autumn and spring; the fewest occur in summer; but they are met with all the year around. It is essentially an urban disease, favored by cold winds and damp. In London, it is more rife and more severe when the cold and rain of autumn follow a hot, dry summer. Damp alone does not explain its frequency, if—as seems to be the case—it is true that it is an urban disease and more severe when the subsoil water-level is low. Often there is no convincing history of chill or damp, but there can be no doubt that exposure to damp cold increases the severity and persistence of rheumatic fever, a point which Beattie proved in the experimental arthritis of rabbits. The entire question of environment undoubtedly requires further study.

Epidemics.—There is a good deal of evidence that there are waves of rheumatic fever; and the character of the disease alters in different outbreaks. Closely allied to epidemic occurrence is the possibility of spread by contagion, and some remarkable examples are recorded. There are difficulties in establishing the truth of this—partly owing to the hereditary tendency, and partly to the influence of atmospheric conditions. It is not uncommon to find two and even three children in a family simultaneously attacked, but this does not prove contagiousness.

Diet.—This does not appear to have any marked effect, and it seems improbable that an excess of meat or carbohydrate is a cause. Excess of uric acid has no immediate bearing on the causation.

Infectious Diseases.—It is possible that an infectious disease associated with sore throat, such as scarlet fever, measles, or diphtheria, may predispose to the rheumatic fever infection.

Pathology.—The pathological changes are for the most part easily understood. The exact nature of the changes produced by the toxins cannot be demonstrated, but the macroscopical and microscopical appearances are quite explicable. The lesions, the carditis, arthritis, nodule formation, pleurisy, etc., are primarily due to the local deposition of the bacteria, and not the result of toxins only. The bacterial infection is widespread and not localized.

From the standpoint of etiology it is remarkable that the pathological

lesions of chorea, which Paine and the writer built up from experimental lesions, supported later by their human investigations, and those of Gordon Holmes, have been recently corroborated by Greenfield and Wolfsohn. Also that the unity of the cardinal rheumatic lesions emphasized from the first by them is now widely accepted.

The entire question of the morbid anatomy has assumed a different complexion since Aschoff and Tawara, Carey Coombs, and Fraenzel have maintained that certain of the lesions—the submiliary nodules—are peculiar to the disease in that they show a special structure which Coombs, Miller and Kettle have reproduced experimentally in rabbits. These scattered foci are found in the various tissues affected. The nodules consisting of fusiform areas, containing a fibrinous matrix, are formed by large spindle-shaped cells lying in the intermuscular trabeculæ of connective tissue. These cells are larger, but otherwise resemble fibroblasts and are often multinuclear. Around their periphery are found plasma cells and mononuclear leukocytes. These nodules are slowly replaced by connective tissue. The writer, who first pictured these lesions in 1899, has confirmed these special appearances, but he hesitates to look upon them as specific tests of the disease without the presence of which we cannot accept any other evidence, a view held by Fraenzel. Such a step is but to substitute a single anatomical feature for the broad scientific lines upon which the etiology of the disease is based and in a recent paper Libman and Sacks state they are frequently absent.

From this infection three types of injury result. (1) The simple type. (2) The fibroid type. (3) The malignant type. In all these types the minute bloodvessels suffer. There may be merely a swelling of the endothelial cells of the arterioles and capillaries or there may be thrombosis from occlusion by endothelial proliferation. Perivascular changes are frequent and in chronic cases cause perivascular fibrosis.

1. In the *simple* type, illustrated by acute rheumatic arthritis, the bacteria are rapidly destroyed by the resistance of the tissues, and the resulting inflammation quickly subsides. If the infection is more severe, or the resistance weaker, death of some part of the affected tissues will occur, and with resolution this dead tissue is replaced by scar formation. The thickening of the mitral valve after acute simple endocarditis illustrates this repair.

The microscopical changes are dilatation and sometimes rupture of the capillaries, with well-marked swelling of the connective tissues in their neighborhood. Where the process is most severe the connective tissues pass from the stage of swelling to necrosis and the area is invaded with leukocytes. With resolution fibroblasts invade the necrotic area and a scar is formed. When these changes occur in the subendothelial tissues of a serous membrane, such as the synovial, pericardial, or pleural, there is a rapid exudation into the cavity of a clear or blood-stained fluid, which later becomes serofibrinous. It is said that suppuration does not occur in rheumatic fever, and this is true if the term suppuration is restricted to the yellow fluid found in pyemic abscesses, etc. In severe rheumatic pericarditis, the condition is in the author's opinion to all intents a *rheumatic* suppuration.

The relation of the bacteria to the exudations is easily understood; yet their absence from the early exudations has more than any other single fact influenced investigators against the bacterial origin of the disease. The diplococci escaping from the minute capillaries are necessarily at first located in the subendothelial tissue, and the endothelium serves as a bar to their escape into the serous cavity. The rapid destruction of the diplococci by tissue cells can be well seen in the wall of the appendix in experimental rheumatic appendicitis. For this reason there is great difficulty in finding them in acute effusions into the joints or other serous cavities. Later, when after a severe infection their toxins have destroyed the protective endothelium and they have escaped into the serous cavities, the leukocytes attack and destroy them. The particular phase in which the bacteria can be easily obtained is the comparatively rare one in which many have escaped into the fluid and the leukocytes have failed or not had time to destroy them.

2. The *fibroid type* of lesion is best exemplified by mitral stenosis. For some unexplained reason, this is more frequent in females. It is a very persistent subacute inflammation, which without causing any considerable amount of necrosis produces a gradual sclerosis. It may be objected that no line of demarcation can be drawn between the simple and fibroid form of inflammation; but there is this practical value in their recognition, that it brings into prominence the difference in prognosis and emphasizes the persistent nature of the fibroid type of the disease.

3. The *malignant* type is best exemplified by certain cases of rheumatic endocarditis in which the microörganisms are not destroyed in the tissues but multiply in the damaged valve and are then disseminated by the blood stream. In the most severe form the vegetations are minute, and yet there are immense numbers of bacteria in them; in those of less severity there are large fungating vegetations in which many bacteria may be present, but in which many are destroyed The reader must look upon the foregoing statements as the interpretation put by the writer upon his own observations. Present opinion favors the view that malignant endocarditis is either entirely non-rheumatic or due to an added infection.

The changes produced by the rheumatic toxins are not known; but one condition is clearly recognized, namely, fatty degeneration. This is sometimes well-marked in the cardiac muscle and also in the convoluted tubules of the kidneys when they are severely attacked. Beattie found amyloid degeneration in 4 cases. Another result is œdematous swelling of connective tissue. The changes in the nervous tissue in rheumatic chorea are becoming apparent as a meningo-encephalitis. Gordon Holmes and the writer investigated 3 cases of fatal chorea and found (1) the diplococcus in the pia mater and brain; (2) vascular and inflammatory changes in the central nervous system and its membranes; (3) changes in the nervous tissue itself, some destructive and secondary to the vascular changes, others due to alteration in the morphological characters of the nerve cells. Fraenzel demonstrated submiliary nodules in the pia mater. Greenfield and Wolfsohn have recently supported in the brain the results of Holmes and Poynton.

General Symptoms.—Onset.—This, especially in childhood, differs widely in its characters. Thus it may be insidious and preceded by indefinite illness, which can be compared to the gradual failure of health that so frequently precedes acute tuberculosis. The following symptoms are met with, among others, in this prodromal stage: Anemia, nervousness, irritability, epistaxis, loss of energy, wasting, headache, sore throat, epigastric pain, and fleeting pains in the joints. The temperature is usually above the normal, *e. g.*, 99.5° F.

Children of rheumatic stock may complain of these indefinite symptoms for long periods before they are attacked by acute symptoms, as for example, in the case of a little girl who was under the writer's care for four years and during that time continually showed one or other of these symptoms. After being chilled, a sore throat followed and after this chorea and mitral endocarditis; since that time she has had several definite attacks of rheumatic fever. The manifestation which commences in this insidious way is most frequently chorea.

When the onset is acute, there may be some definite history of chill or exposure from which the illness is dated, and the first symptoms generally show themselves within a week of this. In the child these are generally sore throat, malaise, fever, pains in the limbs, and prostration. In the more virulent cases shivering, vomiting, and diarrhœa may occur. The symptoms vary in accordance with the organs chiefly attacked; thus multiple and painful arthritis, as in the adult, may be the prominent symptom, or chorea, precordial pain, and dyspnœa. In severe attacks several manifestations may develop within a few days. In some rare cases the subcutaneous nodules have first attracted attention; in others, an eruption.

In the adult the disease may commence in the same insidious manner as in the child; but the acute articular disease is more usual, and when fully developed is characteristic. There may be sore throat, chilly feelings, or even a rigor, and, with these, general malaise, muscular pains, and weakness. The arthritis sometimes appears with great rapidity. There is profuse sweating which is rarely seen in the child, and the sour odor arising from this has long been pointed out as a feature of the disease. If there is excessive sweating a sudaminal rash not infrequently appears on the trunk. The sufferer lies in bed, quite helpless and dreading any movement; many of the larger joints and sometimes the smaller ones are swollen and extremely tender. There may be a red flush over the articulations most severely attacked, and the implication of the tendons and periarticular tissues adds greatly to the distress. Another feature is the rapidity with which the inflammation passes from joint to joint, and also the rapidity with which recovery may occur. Neither in children nor adults is there any characteristic fever. The temperature is moderately raised, 100° to 102° F., and often higher in the adult than in the child. In severe cases the temperature may oscillate considerably. A manifestation which is apt to raise the temperature considerably is a patch of bronchopneumonia.

When much fluid is lost through sweating there is considerable thirst, the appetite is poor, and the bowels constipated. The pulse is usually

more rapid than normal and the wave large and easily compressible, and both in adults and children dilatation of the heart is common. The mind is clear and as a rule acute; not infrequently there is anxiety, mental distress, and insomnia, from the pain. The respiratory system is not usually damaged. The urine is scanty, high colored, and strongly acid; the chlorides are diminished and the urates increased. Hematoporphyrin is sometimes present in considerable quantities.

The interesting question has been raised as to whether rheumatic fever in childhood is the same disease as that which is found in adult life. The writer has followed many patients in whom fresh attacks have occurred in adult life who were also victims in childhood and has convinced himself of the identity of the affection.

Course.—There are few diseases which run a more variable course. In children it is impossible to give any definite rule, for it will greatly depend upon whether the heart is damaged. Then, again, in children virulent cases occur which are never very acute, but which on the other hand never subside; week after week, month after month, one manifestation after another appears, and when death ensues, many months later, it may be truly said that the child was never free from the disease after the onset of symptoms. How closely this recalls the course of a chronic generalizing tuberculosis in childhood need hardly be insisted upon. Nevertheless, there are many cases in which, as in adults, the acute symptoms entirely disappear in three weeks. In the adult it is the frequency of the articular type that gives a more uniform character to the disease. Yet even in this type there is the same tendency to recrudescence—or, as it is generally termed, to relapse—which may protract the illness over many weeks. A fatal termination is rare; when it occurs the most usual cause is acute heart disease; but the most fatal complication is hyperpyrexia.

In this general description no separation has been made, as is so often done, between the disease in the adult and in childhood; for this gives an imperfect idea, more especially because it has been the custom to write of the disease in the adult as if it were *the type*. Nevertheless there is much practical value in due recognition of the special features in childhood, and these are put in tabular form:

1. The onset is frequently insidious, with a prodromal stage in which lassitude, anemia, epistaxis, and epigastric pain, etc., occur.
2. The manifestations are more varied, and the invasion is more general in the child. The most frequent of these manifestations are (*a*) chorea; (*b*) articular pains and swelling; (*c*) tonsillitis; (*d*) carditis; (*e*) erythema multiforme; (*f*) pleurisy and pneumonia; (*g*) subcutaneous nodules; and (*h*) anemia.
3. The occurrence of heart disease is more frequent than in the adult, and for this reason the disease is more fatal in childhood.
4. Articular complications, though frequent, are less severe.
5. Sweating is less common.
6. Nervous symptoms are more often met, notably chorea; but hyperpyrexia is less frequent.

7. There is a greater tendency for the child to drift into the rheumatic state.

8. Subcutaneous nodules are much more common.

9. Malignant rheumatic endocarditis is less common.

10. The anemia is often more profound.

After this preliminary account of the general symptoms it is necessary to study in more detail the important visceral lesions which are considered under the following headings:

1. Those connected with the cardiovascular system.
2. Those connected with the joints, muscles, tendons, and fasciæ.
3. Those connected with the nervous system.
4. Those connected with the respiratory system.
5. Those connected with the cutaneous system.
6. Rarer manifestations: (i) alimentary, (ii) genito-urinary, (iii) miscellaneous.

It may be of assistance in picturing the disease in childhood if the statistics of the most important symptoms found in 500 consecutive cases are given. These symptoms were recorded at the first visit and expressed the first view obtained by an out-patient physician; 248 complained of arthritic pains; 350 had heart disease; 245 had chorea; 137 had throat trouble; 39 had nodules.

Cardiovascular System.—It is the frequent implication of the heart which makes this one of the most formidable diseases in temperate climates; and the study of the heart affections is one of much practical importance. Experimental evidence has shown that a diplococcus which is present in human cardiac tissues damaged by rheumatic fever can produce endocarditis, pericarditis, and fatty degeneration of the myocardium with dilatation of the heart and formation of submiliary nodules both in rabbits and monkeys. These animals may sometimes recover from this acute endocarditis and a healing lesion be found later.

The chief cardiac lesions in man are (1) acute dilatation of the heart, (2) endocarditis, and (3) pericarditis. In almost all the severe cases, however, the damage is a complex one; that is to say, the endocardium, myocardium, and pericardium are affected, and to this condition the term "carditis" is often applied.

There are very considerable differences in the development of these lesions. Sometimes the attack is rapid and severe, and in a short time the heart is terribly injured; in others there is an insidious onset and a gradual downhill progress; while in others the damage is as fleeting as that to the joints. It is accordingly most essential to recognize the earliest warning of heart disease, in order that the patient may be at once placed under strict treatment. This warning is, as a rule, acute dilatation of the heart, the importance of which was insisted on by D. B. Lees. The evidences of it are the following: (1) A slight rise in the frequency of the pulse-rate. (2) The cardiac impulse becomes diffuse and extends beyond the vertical nipple line. (3) The area of deep or relative cardiac dulness is increased to the left, and sometimes to the right and upward. (4) The first sound at the apex becomes short; and the second sound in the pulmonary area is accentuated. (5) A soft

systolic murmur can, not infrequently, be detected internal to the left vertical line. These are the earliest signs of rheumatic heart disease, and this dilatation may entirely disappear.

The rapidity with which dilatation may occur is most remarkable, and this is true both of the adult and the child. The explanation is not easy unless it be associated with some sudden damage to the cardiac nerves and loss of muscular tone. The patient shows but few signs of cardiac dilatation unless it is acute and severe. If he has not been confined to bed there is shortness of breath on exertion, with a sensation of faintness and weakness. When more severe there are muscular weakness, pallor, restlessness, and well-marked dyspnœa.

Allusion has been made to the production of myocardial disease in animals by experimental inoculations of the diplococcus; fatty changes in the cardiac muscle fibres are thus produced, with dilatation and antemortem thrombosis. These facts are important, for there are instances in which death has occurred in man from acute rheumatic dilatation of the heart. In these rare and fatal cases of acute dilatation the symptoms are most urgent. They are dyspnœa, pallor, vomiting, and delirium; the pulse is rapid and feeble, and the heart irregular, with no palpable impulse. The sounds become almost inaudible, although a mitral murmur may be heard in the region of the left nipple. The end may be by sudden syncope. The writer would also emphasize a group of cases in which the dilatation of the heart remains more or less chronic and relapsing. These are intractable in their course, and the patient suffers much from irritable action of the heart, breathlessness and nervousness. A superficial observer may miss the dilatation, and, hearing no murmur, dismiss such a case as functional.

Investigations with the polygraph and electrocardiograph, coupled with the discovery of the focal myocardial lesions, have led to a considerable literature upon disturbances of rhythm, due to invasion of the primitive bundle by the submiliary nodules. In the writer's experience those focal lesions in childhood play a comparatively small part in rheumatic heart disease, which is usually a much more complex lesion. It is in these primarily myocardial cases, however, that now and again striking examples of arrhythmia arise, and in acute virulent carditis heart-block, more or less complete, may be present.

Endocarditis. - The valves on the left side suffer more than those on the right, although in childhood the tricuspid value is not infrequently damaged to a small degree. The tendency for endocarditis to attack the left side is also seen in experimental endocarditis, and experiment further shows that the infection is by way of the coronary arteries. This tells against the view that the special involvement of the left side of the heart is due to the presence there of arterial blood. In childhood multiple valvular lesions are common.

Acute simple endocarditis gives rise to but few symptoms, and it frequently happens that a patient comes under observation with a valvular lesion of which he can give no clear history. On this account there are few more important rules in medicine than "in all cases of suspected rheumatism to examine the heart repeatedly." A rise in temperature

of a degree or more, with pain in the chest, palpitation, and dyspnœa, are suggestive and examination of the heart may show that there is some dilatation.

(*a*) *Mitral Endocarditis.*—The first result of this lesion is regurgitation, which shows itself by a soft murmur audible at the apex and traceable toward the axilla. In some cases there is a prolongation of the first sound before the bruit appears, and another important sign is a persistent reduplication of the second sound at the apex, which points to a thickening of the mitral segments. Lastly, it is not unusual to hear in the child a to-and-fro murmur over the apex.

(*b*) *Aortic Endocarditis.*—The first result of this is aortic regurgitation. Experimental inoculations have caused aortic and mitral endocarditis in animals, and also aortic endocarditis without any other valvular lesion. In man, also, aortic endocarditis may occur as a solitary lesion, although it is more usually combined with the mitral lesion. The physical signs which direct attention to aortic disease are the following: (1) Cardiac excitement; (2) a loss of definition of the aortic second sound; (3) the appearance of a soft diastolic and sometimes also a transient systolic murmur. The aortic diastolic murmur is frequently heard more distinctly to the left of the sternum.

The combined aortic and mitral lesion is a very serious and frequent occurrence in childhood. It is more common in males. The writer would emphasize the importance of this combined lesion and the necessity for listening for the aortic diastolic bruit to the left of and over the sternum. The frequent combination of the two lesions suggests a direct spread of infection in some cases from one valve to the other, a result experimentally demonstrated by Paine and the writer.[1] These cases if severe are not only liable to be fatal at an early age, but also may develop a malignant form of rheumatic endocarditis in early adult life. Acute endocarditis, if it is severe, soon leaves its impress, particularly the aortic lesion in childhood. The anemia is well-marked, and the striking pallor and forcibly pulsating arteries tell their own tale.

On the other hand, although a slight mitral lesion cannot be detected from the aspect of the patient, when it is more severe there is soon noticed a congestion of the bloodvessels of the lips and cheek, which with the purplish hue suggests the lesion before the heart is examined. In acute endocarditis, œdema, if present, is slight; but in children the face is sometimes puffy with an appearance like that of renal disease.

The subacute type of inflammation, which leads to much fibrosis and contraction, is well illustrated by mitral stenosis. This is more frequent in females. So insidious is the onset that it may not attract attention. Nevertheless, a careful study proves that it is associated with continued subacute attacks. In prolonged cases of chorea which drag on for months, and frequently relapse, this stealthy process can often be traced, surely and slowly crippling the heart. The association of chorea with mitral stenosis deserves the closest attention, and in this country is very frequent and of particular interest, because both lesions are far more frequent in the female and suggest peculiarity of the tissues of this sex in their reac-

[1] *Quart. Jour. Med.*, 1912, **5**, 483.

tion to the infection. It is well-recognized that there are cases of mitral stenosis of mysterious origin, some probably not rheumatic. The analysis of 50 cases under personal observation demonstrates the importance of rheumatism in the production of this lesion; 36 were females, 14 males; 3 appeared to be congenital. In 14 cases in which the lesion appeared to be a pure stenosis, 7 gave histories of prolonged or repeated chorea and 6 of prolonged rheumatism. In 33 with stenosis and regurgitation, 22 gave a history of repeated chorea and 9 of prolonged rheumatism. Thus, of 50 cases, in only 6 was no history of rheumatism obtained. Some of the early indications of mitral stenosis are:

1. There may be the signs of a slight mitral regurgitation which disappear to be followed by a progressive abruptness of the first sound. Later this abrupt first sound is noticed in association with a rumbling murmur which is diastolic, mid-diastolic, or presystolic in time, an accentuated pulmonary second sound, and a presystolic thrill.

2. Without any signs of mitral regurgitation, a progressive stenosis, as described above, may develop.

3. Most commonly the signs of stenosis develop in the presence of a persisting mitral regurgitation.

The malignant type of rheumatic inflammation is, in the writer's opinion, illustrated by some cases of malignant endocarditis in patients who have had rheumatic fever. General opinion holds that malignant endocarditis is essentially a different disease; but the evidence in favor of the view that *some* of these cases are rheumatic is very strong. In the first place all members of the micrococcal group to which the diplococcus belongs are capable of producing malignant endocarditis, and it is highly probable that this diplococcus would also produce the same condition. If the histories of cases of malignant endocarditis are investigated a frequent antecedent is found to be rheumatic fever. Some cases, moreover, commence with an onset indistinguishable from this disease, and exhibit during their course manifestations of it; the likeness, in fact, may be so close that even to the end of life it may remain doubtful whether it is simple or malignant endocarditis from which the patient is suffering. The late Dr. Andrewes, Osler, and others pointed out that malignant endocarditis may directly follow rheumatic fever.

These are suggestive facts, although the view that a secondary infection has been grafted upon the rheumatic one can still be maintained for their explanation. When we turn to accurate experiment there is much more definite evidence. Paine and the writer showed in 1902 that in some of these cases of malignant endocarditis, with a rheumatic history, the diplococcus can be obtained in pure culture, and can further produce in rabbits not only simple and malignant endocarditis, but every stage between them. Again, with the diplococcus isolated from simple endocarditis of rheumatic origin, it is possible to produce not only multiple rheumatic lesions but also malignant endocarditis. Lastly, a first inoculation may produce simple endocarditis and another six months later produce the malignant type in the same animal. Further, these experiments teach that the test of the malignancy of endocarditis is not the fungation of the vegetations, but the activity of the diplococci in the

valve. The vegetations may be minute but the malignancy great; the vegetations may be exuberant and yet the case be subacute. Although often called arterial pyemia, suppuration in these forms of malignant endocarditis is rare both in men and animals, although white infarcts are common in both. The virulence of the infection sufficiently explains the "septic" type of these cases. This condition is fortunately rare and doubtless requires secondary causes to aid in its production. Among such causes are previous damage of the valves by former attacks, constitutions debilitated by unhealthy surroundings, the puerperal state, and probably anemia.

The malignant type of endocarditis is to be suspected when there is a persistent and irregular fever and the appearance of the patient suggests severe poisoning. In a considerable number of cases there is a history of previous attacks of cardiac rheumatism, and in some rigors occur, which may be repeated and yet no abscess formation results. One striking feature in the heart is the persistent excitement. The cardiac murmurs may be unusually loud or vary in character. Anemia, sweating, diarrhœa, infarction, and purpura are important features of this type. Some of these cases run a very protracted course, extending over months; others prove rapidly fatal. In other cases the diagnosis between simple and malignant endocarditis may hang in the balance for weeks and then the disease may slowly subside leaving much damage. The malignant type is rare in childhood.

Pericarditis.—The most serious form of heart disease in rheumatism next to malignant endocarditis is pericarditis—not so much on account of its intrinsic harmfulness as on account of the severe type of infection which accompanies it, and the involvement of the myocardium. It is more frequent in childhood than in adult life. The most characteristic examples occur in the first week of the rheumatic attack; but there is no period in which it may not appear. There are three chief types:

1. Simple acute pericarditis; (2) chronic relapsing, adhesive pericarditis; (3) malignant pericarditis.

1. The early symptoms of *acute pericarditis* are a rise of temperature, precordial pain, and dyspnœa. The pulse is excited and the tension low. Pericardial friction is usually detected within twenty-four hours, at the base of the heart, and may rapidly become audible over the entire cardiac area. A more unusual symptom is delirium. The distress in the adult is great, and shows itself in the anxious face and orthopnœa; some children show curiously little discomfort. The great enlargement of precordial dulness, so frequent in pericarditis, is chiefly the result of dilatation, and not of a large effusion. Ill-omened symptoms are vomiting, restlessness, delirium, and lividity, with progressive signs of cardiac failure. A first attack is not as a rule fatal, but pericarditis is the most frequent cause of death in rheumatic fever. The most virulent cases of pericarditis in childhood may occur without any pyrexia as was clearly demonstrated in the London outbreak 1919–1920.

2. The *chronic adhesive type* is frequently found in childhood. This form is subacute, but very intractable, and gives rise to complete and dense pericardial adhesions. It may be associated with mediastinitis,

pleuritis, and sometimes also peritonitis; and it is probable that some of those remarkable cases named multiple serositis by American writers are the result of rheumatism of this type.

3. The *malignant type* is rare and best illustrated by the account of a fatal case: C. D., aged seven years, had an attack of rheumatic fever when six and a half years of age, from which he recovered. Three weeks before he came under observation he was attacked by pains in the elbows, shoulders, wrists, and fingers, followed a few days later by precordial pain and dyspnœa. His condition from the first was serious. There was advanced mitral disease, he was pale and thin, and there were numerous rheumatic nodules. His illness extended over three months, and throughout there was irregular fever, each day the temperature rising to 102° to 104° F., and until the last week it never reached normal. The heart was persistently excited, and the idea of pericarditis was repeatedly suggested, but no definite friction rub could be detected. Crops of nodules came out and the boy gradually sank and died. The necropsy showed a pericardium greatly thickened and generally adherent, partly with subrecent adhesions and partly with recent plastic exudation. The left pleura showed a recent pleurisy. The mitral valve showed thickening and a few recent vegetations, as did also the tricuspid; the other valves were normal. In this case, as shown by the extensive pericarditis and great thickening of the pericardium, there had been a persistent and progressive pericarditis extending over probably the entire three months.

Blood.—Extreme, even fatal, anemia may result. In severe cases there may be great hemolysis. During the acute phase there is a rapid fall in the number of the red corpuscles, and this anemia may be very obstinate. A moderate leukocytosis is frequent, and there is, in exceptional cases, a marked increase. It is difficult and exceptional to demonstrate the diplococci in the blood, for they are localized in the various lesions. This can, however, be done when the disease is very severe and generalized, and they can also occasionally be detected in the polymorphonuclear leukocytes.

Arteries, Capillaries, and Veins.—Legroux recorded acute arteritis, the inflammatory changes commencing in the intima immediately beneath the lining endothelium. Barre described an acute arteritis of the brachial artery attributed to rheumatic fever. In the subacute lesions, a perivascular fibrosis occurs which must, by contracting the lumen of the minute arterioles and capillaries, interfere with the circulation of the affected part—synovial membrane, pericardium, etc.—and thus assist in contributing to the indolent nature of the lesions. It is an interesting speculation whether this process may not, when on an extensive scale, be a factor in arterio-capillary fibrosis.[1]

Phlebitis with venous thrombosis may be a result of the rheumatic infection. In 10 cases under the writer's observation this took place in the large tributaries of the superior vena cava. This complication is

[1] In a rabbit by intravenous inoculation, Paine and the writer have produced aortitis with calcification of the first part of the aorta. The lesion occurred in three weeks and there was also multiple arthritis.

to be suspected when a localized œdema of a limb, or of the chest or face, appears somewhat suddenly. If with this there is tenderness along the course of the veins, dilatation of collateral vessels, and the sensation of a thick cord in the position of the vessels, the diagnosis becomes assured. French observers have stated that its occurrence is more frequent in the lower extremities. Recently the writer had under his care a case of severe thrombo-phlebitis of the lower end of the inferior vena cava, the first example in his experience. The patient was a lad with severe chorea and pancarditis.

Articular, Fascial, and Muscular Involvement.—Arthritis is the most striking evidence of rheumatic fever and in adult life comes into such prominence that it has been looked upon as a disease in itself, and termed "acute articular rheumatism." The objection to this term is very evident. The arthritis is generally polyarticular, and the larger joints, knees, ankles, shoulder, and hips are most frequently attacked. It may, however, be monarticular. No distinction can be drawn between arthritis deformans and rheumatic arthritis from the frequency with which the larger joints are attacked, for in childhood the small articulations of the hand and fingers are often the seat of rheumatic inflammation and the hands may closely resemble the appearance of the acute form of arthritis deformans. In some cases in childhood the great-toe joints resemble those of a gouty man. The acute inflammation and the implication of the tendons surrounding the joints render the arthritis extremely painful. There may be much or little exudation, or there may be great pain with no definite signs of arthritis at all. The articulations are hot and tender, and there is often a red flush over them.

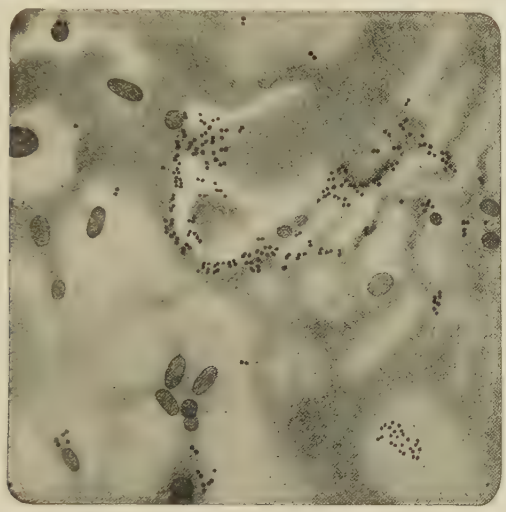
In animals arthritis is easily produced by intravenous inoculation of the diplococcus, and in them, too, the neighboring tendons are involved. The stages of the process in animals can be studied in all phases. There is at first a deposition of the micrococci in the subendothelial connective tissue of the synovial membrane, and, with this much capillary dilatation, even capillary hemorrhage. The endothelium is phagocytic, and numerous leukocytes pass into the subendothelial connective tissue, and by these means the micrococci are destroyed. The exudation, at first clear or blood-stained, later becomes fibrinous, and if the arthritis is very severe much of the endothelium is destroyed and many leukocytes and endothelial cells, together with diplococci, pass into the synovial cavity. The capsular tissues swell and become gelatinous in appearance. A local inoculation of the micrococcus into the knee-joint in a rabbit will, as Shaw pointed out, sometimes cause an endocarditis.

Because rheumatic arthritis is often a simple synovitis, and probably because the diplococci are rapidly destroyed in the tissues, it usually runs such a rapid course. A condition of osteoarthritis and also a chronic synovitis can be produced by the *Diplococcus rheumaticus* in rabbits. Paine and the writer in 1910 showed two striking examples, one of which is in the Hunterian Museum. Beattie and Yates recorded not only relapsing arthritis and osteoarthritis changes, but demonstrated the micrococcus in the synovial tissues of rabbits, at intervals from some weeks to twelve months after the onset of the arthritis. Further, they demon-

strated the micrococci in the synovial membranes after intravenous inoculations. These results strongly support the writer's contention that the infective agent may remain quiescent, but not destroyed, for long periods of time in the human tissues.

The tendons are often damaged by an inflammation of their sheaths; gangliform swellings may appear, and as a sequel painful adhesions sometimes result. *The periosteum* also may be attacked and painful; fixed, periosteal nodes develop.

FIG. 25



The *Diplococcus rheumaticus* in a rheumatic nodule.

The most interesting and remarkable of the inflammations in the connective tissues are the *subcutaneous nodules*. These are the result of a local deposit of the diplococci in the subcutaneous tissues. The writer has shown with Paine a section in which the diplococci were actually found in a minute bloodvessel in the tissue of a human nodule. The usual changes result, viz., swelling of the connective tissue, dilatation of the blood capillaries, exudation, and necrosis of the most damaged area. The microörganism is destroyed by the living cells. These nodules are not, as so often termed, fibrous nodules, but inflammatory exudations. When the inflammation is chronic, some fibroid change may occur in the necrotic area. Nodules can be produced in rabbits by injection of the diplococcus. In size they vary from a pin's head to an almond, and are often better seen than felt, if the skin over them is gently stretched and the light is thrown obliquely. In rare cases the skin over them is reddened and they become adherent to it, and slightly tender; but it is interesting how little discomfort these nodules usually cause, even when developing rapidly and in numbers. This manifestation is much more common in childhood and varies in frequency with different outbreaks. The nodules should be looked for over the bony prominences and along

tendons, as, for example, upon the bony processes around the elbow-joint, and edges of the patellæ, along the tendons of the extensors of the fingers and toes, over the parietal and occipital bones, around the ankle-joints, over the vertebral spines, along the crests of the ilia, and on the spines of the scapulæ. They may appear and disappear in three days, and cannot for this reason be essentially fibrous.

Their great clinical interest lies in their frequent association with severe cardiac rheumatism. This is not invariable for occasionally they are almost the only rheumatic symptom, but, as a general guide, the rule (Cheadle) that rheumatic nodules are associated with severe heart disease is a valuable one. Of 33 cases showing rheumatic nodules 12 were fatal, 17 had severe heart disease, 4 moderate heart disease and 2 were free from heart disease. Their diagnostic value is considerable, for although nodules are met with in arthritis deformans, gout, and erythema nodosum, these generally differ in their distribution or appearance. They must as a rule be searched for, although there are exceptional instances in which the parents or patient have made the discovery.

A condition upon which accurate knowledge is more difficult to obtain is that of inflammation of the muscles and their fasciæ. Froriep described the occurrence of localized swellings in the muscles. These swellings are localized connective-tissue inflammations which when chronic produce fibrous nodules or strands in the muscular tissue. These nodules or strands may hamper muscular action or press upon nerve fibres. In rheumatic fever, A. E. Garrod noted the occurrence of a node of this kind in a child, and the writer has seen a similar one in the left pectoralis major. It is probable that the stiff neck, pleurodynia, lumbago, and tender feet are the result of changes of a similar nature.

Manifestations in the Nervous System.—The disease frequently damages the nervous system, and its most severe form has been called "cerebral rheumatism." Children of rheumatic parentage are often highly nervous and prone to headaches, night terrors, and insomnia.

Chorea.—There is perhaps no more remarkable condition than chorea, and although its association with rheumatism has long been noticed, yet the complete explanation of its symptoms remains a most difficult problem because of the rarity of opportunities for investigating it after death. These facts, however, have been ascertained:

1. Chorea is associated very frequently with rheumatic fever.
2. The association is of such a close nature that chorea, when rheumatic, must be looked upon as a manifestation of that disease.
3. The more carefully the examinations of the brain are conducted after death the more frequently are some definite lesions found.
4. Investigators have isolated micrococci from the meninges, cerebrospinal fluid, and brain, in fatal chorea.

In 1899 Westphal, Wassermann, and Malkoff, from a fatal case of carditis and chorea, isolated a minute diplococcus which produced polyarthritis in a series of 80 rabbits. In 1900, Paine and the writer observed remarkable twitching movements in a rabbit following intravenous inoculation of a diplococcus obtained from a case of fatal rheumatism. This microörganism was similar to that described by Wassermann.

Similar movements in rabbits have been observed by Fritz Meyer of Berlin, and Beattie of Edinburgh; in both cases they were results of inoculations of a similar microörganism. It is an interesting fact that such movements should have followed these inoculations and that the microorganisms have been demonstrated by Paine and the writer in the pia mater and in the blood capillaries passing into the motor cortex of the animal's brain; also that they have isolated the diplococcus immediately after death from the cerebrospinal fluid of further cases of rheumatic chorea, and by cultures from one of them have produced in rabbits not only arthritis, but also endocarditis and pericarditis.

Gordon Holmes and the writer investigated 3 fatal cases of chorea, including 1 in pregnancy, and found these changes in the nerve cells: (1) Practically all the cortical cells were affected, being swollen and distended; their tigroid had partly disappeared and their nuclei stained more deeply than normal. (2) In some of the cells the nuclei were shrunken and deformed with the outline of the cell bodies indistinct. There were also small areas of cortical softening. Fraenzel demonstrated submiliary nodules in the pia mater. Greenfield and Wolfsohn have recently reviewed the pathology and contributed a detailed investigation of a fatal case. They comment upon the resemblance of the lesions to those in epidemic encephalitis and describe general vascular changes in the brain, such as cortical thrombosis and dilated blood capillaries with proliferated endothelial linings; also small-celled infiltrations in the tissues immediately outside the bloodvessels and their perivascular lymph spaces. These changes were wide spread particularly in the internal capsule and basal ganglia, together with irregularly distributed nerve-cell degeneration. They conclude that the pathological basis is a diffuse encephalitis affecting chiefly the corpus striatum and involving the cortex and the pia-arachnoid.

The explanation that naturally suggests itself is that the microörganisms gain a foothold in the meninges and brain and probably also in the spinal cord, where, partly by the toxins produced and partly by the local lesions, they give rise to the phenomena. Whether, as Triboulet (Père) maintained, the peripheral nerves also suffer in chorea is uncertain. At present it seems inadvisable to claim all cases of chorea as rheumatic, for it is but reasonable to suppose that other allied microörganisms may possibly in a lesser degree produce chorea. Upon this point more evdience is needed. The statistics of the writer upon the relation of chorea and rheumatism are as follows: Of 500 consecutive cases of rheumatic heart disease and chorea in childhood, 220 came for chorea. Of these, 122 had obvious organic heart disease; 38 had dilatation with rheumatic arthritis and pain; 10 followed immediately upon a sore throat; 20 gave a decided family history; 15 were attributed to fright and shock, 2 developing heart disease later; 15 gave no clue, 2 succumbing later to rheumatic heart disease.

Chorea is far more frequent in childhood than in adult life. It appears at any period in the course of an attack of rheumatism. The writer's youngest patient was aged two years and nine months; she began to show signs of mitral stenosis at three years.

"*Cerebral Rheumatism.*"—The most severe form is associated with hyperpyrexia, and is, in England, usually termed rheumatic hyperpyrexia. These cases are fortunately rare. The Continental term "cerebral rheumatism" is preferable to rheumatic hyperpyrexia, for grave symptoms may arise without extreme fever; and, although the fever is a most important sign, the general symptoms are not entirely due to it, but are also a result of the profound toxemia.

The onset occurs as a rule in the third or fourth week of the active disease, although it may supervene after the temperature has been normal for more than a fortnight. Unfortunately there are no means of discovering in what cases this particular danger exists, and it may supervene so rapidly that the medical attendant is completely taken by surprise. Warning symptoms are headache, delirium, sleeplessness, and vomiting. In some cases there is cutaneous hyperesthesia; in others frequency of micturition. When the condition is more advanced the mental disturbances become more serious, semiconsciousness supervenes, with spasmodic twitching and irregular breathing; the pupils are contracted and the eyes widely open; the pulse increases in rapidity and the face becomes livid. The temperature may rise gradually and then leap up to 108°, 109° and 110° F., or it may rise abruptly from the normal to hyperpyrexia. In some cases the other rheumatic symptoms abate when this condition supervenes. Death occurs in over 50 per cent. of the cases which are not promptly treated, and is almost invariable if the temperature rises above 106° F. Many patients die even with prompt treatment. Cerebral rheumatism is not always of this exceedingly severe type, and cases occur in which dangerous symptoms, such as delirium, high but not extreme fever, and headache, are met with and then abate, and this may occur more than once in a single attack. It is exceptional to find any gross cerebral lesion after death.

Spinal Lesions.—There is much uncertainty about these lesions, and the question is complicated by the occurrence of arthritis as a result of nervous diseases. This makes it difficult to decide in doubtful cases whether the primary cause is a nervous one and the arthritis a symptom of it, or whether the nervous disorder and the arthritis are both results of some general infection such as rheumatic fever. An interesting example of a probable rheumatic paraplegia is quoted by A. E. Garrod. The patient, a case of Alexander Raynault's, was a man, aged twenty-four years, who had passed through repeated attacks of rheumatic fever. His illness commenced with loss of power in the legs and sphincters, and was looked upon as an acute diffuse myelitis. Recovery of power commenced to show itself in two days, and was followed by multiple arthritis, and this in turn by endocarditis, and lastly by pneumonia and pleurisy.

Peripheral Nerve Lesions.—The peripheral nerves also suffer, and a symmetrical peripheral neuritis or a local neuritis may result. This may give rise to well-marked sensory symptoms such as tingling, numbness, and partial anesthesia; or to rapid muscular atrophy and trophic changes. Severe neuralgia, not infrequently affecting the scalp, may also be a result, and in some of these cases fugitive swellings, apparently œdematous, may be detected over the tender points.

Respiratory System.—The occurrence of tonsillitis has been noted for many years. Striking examples occur which leave little room for doubt that the throat is one channel of infection. In 1900 Paine and the author isolated from a patient with tonsillitis a diplococcus which resembled in all respects the one already isolated from such rheumatic lesions as endocarditis, pericarditis, and arthritis; it led to similar experimental results, suggesting that invasion could be through that channel. It is hazardous to draw deductions as to the causation of rheumatic fever from cultures taken from the throat alone, but there is now practically a consensus of opinion that certain "streptococci" found in the throat are very liable to produce multiple arthritis and carditis on experimental intravenous inoculations in animals.

The usual appearance of the "sore throat" is a diffuse redness with some swelling of the tonsils and the palatal mucous membrane. Follicular tonsillitis is also met, and, less commonly, a condition closely resembling diphtheria, or that found in some cases of scarlet fever. The tonsillitis in rheumatic fever is often but slightly painful, and for that reason easily overlooked. In childhood it may occur as an isolated event in the prolonged history of a rheumatism, and may be then interpreted as a successful effort on the part of the tissues to destroy the invading microorganisms, either entirely at the local site, or to such an extent that those which enter the system are unable to produce detectable visceral lesions. There is no relation between the severity of the sore throat and the gravity of the rheumatic attacks. Another point worthy of attention is that chronic enlargement of the tonsils with or without adenoids is very frequent in this disease. In such tonsils there may be deep foci, and such infected areas may be concealed beneath the stump of an amputated tonsil. Should an operation be done upon the tonsils in a state of active angina, an attack of rheumatic fever may follow, the first symptoms showing about the third day. Enlargement of the cervical glands with tenderness is often associated with rheumatic angina.

Lungs and Pleura.—Pleurisy is common and can be experimentally produced in animals. It is met with in the majority of cases in which there is severe pericarditis, and adds greatly to the suffering of the patient. It is a serofibrinous inflammation which in the process of resolution is very liable to give rise to adhesions. These are frequent between the pericardium and adjacent surfaces of the pleura in fatal pericarditis, and the signs of pleurisy in that situation are characteristic. In addition to pain in the chest, there is pleuro-pericardial friction. Pleuro-pericarditis is a painful complication of pericarditis. Should it occur alone it must not be mistaken for pericarditis itself, for the prognosis is far less grave in pleuro-pericarditis, where the outer surface only of the parietal pericardium is damaged, than in pericarditis, essentially a disease of the heart itself. In exceptional cases the effusion may require tapping and the diplococcus has been isolated.

Pleurisy frequently occurs without pericarditis, but how often as a solitary rheumatic manifestation is disputed. Nor does one see how an agreement can be arrived at, since rheumatic pleurisy tends to get well and seldom needs surgical measures. Nevertheless when the statement is

frequently made that simple pleurisies are tuberculous, this form needs to be considered. There is nothing peculiar in the symptoms.

Pneumonia occurs in severe types of rheumatic fever, and results in animals from experimental inoculation. It is usually a bronchopneumonia. The temperature rises rapidly, and an unusually high fever, apart from hyperpyrexia, should suggest the possibility of pneumonia. This is a point of practical importance, for there is a natural desire not to distress a patient by movement, and the pneumonia may be overlooked. There may be a considerable area of collapse around the pneumonic patch, giving the impression of a condition more extensive than that which actually exists. The consolidation may clear with great rapidity, although fever may remain because of other manifestations.

Acute pulmonary œdema is very rare and in the 3 cases observed by the writer all were complicated with carditis. One recovered; 2 rapidly died. The necropsies showed an œdema comparable to that in nephritis, involving the upper lobes of the lungs more than the lower. The kidneys do not show gross changes. There is a possibility that very large doses of sodium salicylate may predispose to this condition.

Bronchitis.—The evidence of a rheumatic bronchitis is not certain.

Laryngeal Affections.—Rheumatism of the crico-arytenoid joints, with some laryngitis has been recorded by Hirsch and other writers.

Cutaneous Manifestations.—The most common eruption is a form of erythema—erythema marginatim or papulatum. *Erythema marginatum* appears over the trunk and extremities in the form of rings, sometimes mistaken for ringworm or erythema iris. The rings are pink, slightly raised, and encircle skin of a livid color. In size they vary considerably, and several may coalesce into large gyrate areas. This eruption gives few symptoms but there may be some local tingling and irritation. As the rash fades it leaves a stain, and if, as is sometimes the case, there have been hemorrhagic areas, these discolored patches last for a long time. In *erythema papulatum* the papules vary in size, are usually symmetrical, come out in crops (especially upon the dorsal surfaces of the extremities), and fade, leaving a stain. In color they are bluish-pink. In both these eruptions there is often a hemorrhagic element. Bullous eruptions are also met with in which the bullæ contain a clear fluid. Purpura is also seen during acute attacks. Small macules appear particularly over the lower extremities, and occasionally a curious irregular net-work is formed by interlacing lines of purpura. Sometimes the purpura is severe and accompanied by sanious bullæ.

A *scarlatiniform* eruption has been described. In 1 case there was a general erythema of the scarlatinal type, but lacking in the punctiform character. There was no reason to believe that it was scarlet fever, and there was no desquamation, although this would not disprove the rheumatic origin of the rash.

The relationship of *erythema nodosum* to rheumatic fever is still disputed. The position stands thus: Erythema nodosum appears to be frequent in the rheumatic, and in some instances to be associated with such active signs as endocarditis and arthritis. On the other hand, many cases of erythema nodosum run a course of their own, and appear to have

no relationship with rheumatism, and for this reasons some believe it to be a special disease closely allied to, but not identical with, rheumatic fever. Others believe it to be rheumatic, while others again look upon it as symptomatic of various infections and among these the rheumatic. Further investigations are required. Erythema nodosum may be general although rarely so, and with it there may be subcutaneous nodules over which the skin is not reddened, and which are the results of great vascular hyperemia and serous exudation.

These eruptions may be the first symptom of active rheumatism, or may appear during the course. As with other manifestations the frequency of cutaneous lesions differs in different epidemics.

Rarer Manifestations.—*Alimentary System.*—It has been frequently noticed that rheumatic children have a weak digestion and are liable to "bilious attacks" and mucous diarrhœa; but it is difficult to assign a part in their causation to active rheumatism, and it is doubtful whether the epigastric pain that rheumatic children so often mention is gastric in origin. Experimental investigations also show that a mucous diarrhœa is not uncommon in animals. In adults there are cases in which there is acute gastric dilatation or distention of the colon, with almost unsupportable outbursts of pain. If with these there is associated carditis the condition is serious and the illness may be very prolonged or even fatal. Peritonitis is more common and in fatal cases of rheumatic fever a chronic peritonitis may be found around the liver and spleen. On one occasion the writer heard loud peritoneal friction during life; and in another there was complaint of abdominal pain over the upper segment of the abdomen where peritonitis was demonstrated after death. It has been produced experimentally, and, further, the micrococcus has been isolated from the exudation in man. Certain writers have maintained that there is an association between rheumatic fever and appendicitis but the writer has never found acute changes in the appendix in a fatal case of rheumatic fever and the frequency of the two diseases raises the possibility of coincidence.[1] In 1911 Paine and the writer produced appendicitis in rabbits by the intravenous inoculation of the diplococcus from a case of rheumatic fever. The organisms invaded the appendix from the peritoneal surface. In 1912 the first complete proof of a cause of appendicitis was published by Paine and the writer working with the *Diplococcus rheumaticus*. The papers published in Researches on Rheumatism throw much light on the pathology of human appendicitis.

Genito-urinary System.– Among the rarer incidents is acute nephritis, and experimental investigation has thrown considerable light upon this subject. The diplococcus is freely excreted in the urine of animals that have been injected intravenously, and can be isolated from the urine of patients suffering from acute rheumatic pericarditis. In rare instances, as observed by Paine and the writer, and Vernon Shaw, acute nephritis may result from these inoculations. The former have observed it in rabbits and in a cat. The cat within three days of inoculation developed profuse hematuria from which it eventually made a perfect recovery; during this period the urine swarmed with diplococci. After recovery

[1] *Proc. Roy. Soc. Med.*, Path. Sec., 1911, **5**, 19.

the animal was killed and no trace of endocarditis was discovered, which excluded the possibility of a gross infarct.

Acute nephritis has been recorded in man (George Johnson, Leyden, Dickinson, Hayem, Lees, and Garrod). Some writers are sceptical as to the occurrence of acute rheumatic nephritis but of its existence the writer has no doubt and he has met with several instances in childhood. Another point of interest is the occurrence in man of large white kidneys in some cases of malignant endocarditis, and of nephritis with continuous hematuria in others, to which special attention has been drawn by Litten. A condition of large white kidney has been produced by experimental inoculation of the diplococcus into rabbits, occurring with malignant endocarditis.

A far more difficult question is the possible influence of rheumatism in causing *chronic renal disease*. Leyden directed attention to the fact that although acute rheumatic nephritis as a rule clears up rapidly, there are cases which drift into a chronic nephritis. Can rheumatism in addition to this, produce a change in the kidney, one which is never acute, but which terminates in a granular condition? It must be admitted that very many acute cases show no changes in the urine so far as albumin and blood are concerned; yet in rheumatic fever, and even in chorea, albuminuria is not very rare, especially when the patient has not had sufficient rest. This albuminuria rapidly disappears, but may recur on exertion and resemble orthostatic albuminuria.

It is conceivable that in such cases there may be insidious damage to the kidney which slowly increases in a manner comparable to the slow contraction of the valve in mitral stenosis, and Beattie has observed experimental interstitial nephritis. This, too, is not altogether hypothetical, for a granular condition of the kidney is frequently met in necropsies upon mitral stenosis and is more frequent in women.

The Influence of Pregnancy and the Puerperium.—As a general rule pregnancy and the puerperal state tend to produce a grave type. The severity of chorea in pregnancy is well recognized. and there is little doubt that in a considerable number of such cases there has been a definite history of rheumatic fever or chorea in earlier life. French and Hicks found in 29 consecutive cases a history of previous rheumatism in 19 and 15 of the 19 had suffered from chorea. The same intensification is sometimes noticeable with rheumatic carditis, which may become active and develop into the malignant type and prove rapidly fatal. Paine and the writer observed that a rabbit which had recovered from rheumatic fever with endocarditis and arthritis died rapidly on reinfection, when pregnant, from malignant aortic endocarditis. The same type of endocarditis was noted by Shaw under similar circumstances.

Mastitis.—Still directed the writer's attention to the possibility of a rheumatic mastitis in childhood, and 4 patients have been under observation with active rheumatism and mastitis of the left breast.

Thyroiditis has been observed; and in chorea, there is sometimes complaint of pain in the thyroid gland, and, more rarely, some swelling and tenderness is observed. *Parotitis* has also been recorded.

Lymphadenitis.—In all cases of fatal rheumatic pericarditis the mediastinal glands are considerably enlarged, and in some cases of tonsillitis

with rheumatic fever the cervical glands are swollen. It is exceptional to meet with a general enlargement of the lymphatic glands.

Eye.—Conjunctivitis, erythematous and phlyctenular, is met with, and in rare cases acute iridocyclitis complicates an acute attack. This latter lesion is occasionally produced in rabbits by the intravenous inoculation of the diplococcus.

Diagnosis.—The diagnosis of the articular type and in an adult is a simple enough matter. The multiple and painful arthritis, the sweating, dilated heart, metastatic character of the articular lesions, and the reaction to salicylate of sodium, with rapid subsidence of the arthritis, all combine to make the disease a very characteristic one. It is, however, a very different matter when the disease is abarticular, the onset gradual, or the symptoms unusual; and although this division is in no sense a scientific one it will serve to make this part of the subject clearer if the diagnosis is first considered in the child and then in the adult.

1. **In Childhood.**—In many cases children with a rheumatic family history drift *gradually* into rheumatic fever. They are "out of sorts" for some weeks, with malaise, wasting, epistaxis, nervousness, slight fever, and fleeting pains. Such an occurrence should suggest the possibility of an acute attack in the near future. Fever, multiple arthritis, and cardiac dilatation in a child usually mean rheumatic fever.

One serious mistake is to confuse *acute osteomyelitis* and rheumatic fever, for a life may be lost by procrastination. From the first, acute osteomyelitis is a serious condition. There may be shivering or actual rigors, the pain in the affected limb or limbs is very severe, and the region of the inflammation rapidly becomes swollen and sometimes brawny. Importance must be attached to the position of greatest tenderness—which is over the epiphysis and not in the joint—to the high fever, prostration, and delirium. The best safeguard against error is the knowledge of its possibility.

A more difficult problem is sometimes offered by *acute anterior poliomyelitis*, for in the early phase of this disease there is often a good deal of pain and fever. A loss of reflex, if it occurs, is a valuable aid, as also marked wasting. It is the early stage that there may be great doubt and an opinion may need to be given with caution. There is no swelling of the joints or heart disease in anterior poliomyelitis.

A mistake more common than would be expected is that of confusing *infantile scurvy*, which is not uncommon under two years of age when rheumatic fever is exceedingly rare. In a doubtful case at this age scurvy should always come first to mind. The gums must be examined for ecchymoses, the bones for periosteal swelling, and the skin for purpura. Hemorrhages from the kidneys or from mucous surfaces, pallor of the face, and extreme tenderness, are suggestive of scurvy. The heart is not damaged, and, when once this condition is remembered, the diet and the result of its alteration will soon solve any doubt.

Congenital Syphilis.—There are two conditions which may give rise to confusion. The first is the comparatively uncommon pseudoparalysis. In some instances this is accompanied by epiphyseal swellings; in others no swelling can be detected. Here again it is the pain which gives rise to the error. An inquiry into the history, the complexion of the child,

its age, and the presence of the stigmas of congenital syphilis, will prevent this error. The fact that the swelling is epiphyseal and not articular is also important. The second condition occurs in older children, syphilitic arthritis. There are different forms of this, and although many joints may be damaged the knees are the most frequently attacked. The course is slow and the condition not very painful. It is a lesion associated with keratitis, peg teeth, and syphilitic deafness. The heart is usually spared, and there is no history of previous rheumatic fever. The Wassermann reaction is of additional assistance.

Gonococcal arthritis, if due to infection from the mother, shows itself in the first five weeks of life, and is usually associated with ophthalmia. It is uninfluenced by treatment with salicylates. Gonococci may be demonstrated in the exudation.

It may seem almost fanciful to mention *appendicitis* as a cause of confusion, yet in childhood this difficulty may arise. The particular cases are those in which rheumatic fever affects only the right hip when children may refer the pain above Poupart's ligament over the region of the appendix. These cases are unusual, and as a rule other joints are soon affected or other rheumatic manifestations appear.

Acute Tuberculous Arthritis.—Clinically, this is indistinguishable from the rheumatic, but proof has been furnished in some cases by the demonstration of tubercle bacilli in the joints. As a rule the differential diagnosis turns upon the presence of active tuberculosis elsewhere and the absence of any history of rheumatic fever.

There is a group of cases of *multiple arthritis* which has been described by Still. This form commences usually in an insidious manner before the second dentition, although in exceptional cases the onset is acute. There is a progressive enlargement of the joints, mainly periarticular and the effusion as a rule is inconsiderable. The muscles waste and contractures are not uncommon. One feature is an enlargement of the lymphatic glands, which bears a distinct relation to the affected joints; and another is enlargement of the spleen, which occurs with considerable frequency. Anemia and sweating with pyrexia occur and although heart disease is exceptional, adherent pericardium has been found; and in other cases endocarditis has been detected.

Arthritis Deformans.—This is rare in childhood. Some writers consider the arthritis just described as a form of this; but, in addition, cases occur in which there are lipping and bony outgrowths, and in which the muscular wasting is extreme, and yet the heart escapes. Arthritis may occasionally be a prominent symptom in posterior basic meningitis. The results of lumbar puncture may give the diagnosis.

2. **In adults.**—*Arthritis deformans* and *gout* sometimes cause difficulty. In arthritis deformans the marked implication of the smaller joints, the course, the failure of salicylate treatment, the muscular wasting, and the rapid action of the heart (which is generally free from organic disease), are some of the main points relied upon for diagnosis.

Gout.—The differential diagnosis between rheumatic fever and acute gout is generally easy. Gout is more usual over thirty. The frequent implication of the great-toe joint and frequent escape of the larger joints,

the occurrence of tophi, and the absence of heart disease, are striking differences. The habit of the patients are also suggestive.

Gonococcal arthritis may lead to error. The history of urethritis is a cardinal point. The arthritis is stubborn, the plantar fasciæ are frequently implicated, and iritis is more frequent. The heart is less liable to suffer, and the salicylates have but little influence.

In adults and in children *influenza* may cause difficulty. The severe pains and dilatation of the heart cause confusion, and the frequent occurrence of a sore throat adds to the similarity. Arthritis is not very uncommon as a result of influenza. In the majority of cases the onset is more abrupt than in rheumatic fever, and when the onset of the latter is more acute than usual the multiple arthritis develops rapidly. On the other hand, the arthritis of influenza is usually a late result.

Pyemia with suppurative arthritis, both in adults and childhood, may be most difficult to distinguish especially in some cases that follow acute otitis media. The comparative rarity, however, compared with the frequency of rheumatic fever is important. The prostration and general poisoning are more profound in pyemic arthritis. Foci may form in the subcutaneous lesions and break down into small abscesses. Rigors and a high fluctuating temperature are further warnings. The heart becomes rapid and feeble, and although endocarditis is not so frequent, suppurative pericarditis may supervene most insidiously without the appearance of any pericardial friction.

Pneumococcal arthritis is usually sufficiently severe to demand an investigation of the fluid, and from this the pneumococcus may be located; although perfect recovery may occur, the type is more septic and usually only one or two joints are affected.

Malta fever differs in the occurrence of sudden outbursts of pyrexia with severe prostration, alternating with intervals of comparative health. The *micrococcus melitensis* gives a definite serum reaction (Wright).

Acute rheumatic arthritis in one joint may be mistaken for a sprain. This is a not very uncommon error, sometimes upheld in spite of the appearance of a "sprain" in the other ankle.

Hemophilic Arthritis.—The sudden hemorrhages into the joints must be distinguished by their abrupt onset and the family history.

Subacute Bacterial Endocarditis.—The difficulty in the present position of the bacteriology of endocarditis has been discussed but the practical point for the physician is clear. Whatever may be the views of the pathologists it is evident that whenever an endocarditis shows signs of a progressive course the outlook is very grave, and it follows that the signs of malignancy must be carefully sought for. Whether the illness is called a progressive rheumatic endocarditis or by any other name is of secondary importance. Active valvular disease would convey to friends of the patient a sufficient explanation.

Prognosis.—This is a complicated matter, and often the attempt at prophesy is a failure, or at best suggestive of the Delphic oracle. It is concerned with estimating the danger to life, the general outlook for the future, and the liability to recurrence.

1. The *danger to life* in a first attack is not great. Hyperpyrexia is generally accepted as the most dangerous complication, and it is not

possible, if this supervenes, to foretell the issue. Acute carditis may prove fatal in a first attack, and its occurrence in a young and delicate child points to caution in the prognosis.

2. In judging the future, the *age* stands first. In general, the younger the patient the greater liability there is to further attacks and to cardiac complications. The surroundings are important; the child of poor parents who is living in an unsuitable climate and is badly fed and clothed is heavily handicapped. The nature of the attack is another consideration. The insidious form in the young, in which one manifestation appears after another for weeks and months, is most unfavorable. Carditis under six years of age with rare exceptions means the ruin of a life. Combined valvular lesions in childhood are very serious.

3. In calculating the chance of another attack the age is important, for the younger the patient the greater the liability. A strong family history of rheumatism points to an increased liability, and if the circumstances or occupations are unsuitable the danger of more than one attack occurring is enhanced. The physician will often find it difficult to say whether the symptoms are the result of a new infection or are the result of a fresh outbreak of a slumbering first infection.

Treatment.—This, although in some respects encouraging, is on the whole unsatisfactory. The disease may respond to treatment in a way which is almost magical; but cardiac complications in childhood are the despair of the physician. The subject divides itself into three parts: (1) The preventive treatment. (2) The treatment of the disease itself. (3) The management of those with an inherited tendency.

Prevention.—The importance of preventive measures is outstanding. In England the vast proportion of organic heart disease in the young is rheumatic. The American physicians are pushing forward with the organized care of cardiac patients and in England efforts are being made to approach the problem of rheumatism from every direction. These practical steps are evident.

1. The education of parents and employers in the chief dangers of rheumatic fever.

2. The education of students in the clinical aspects, particularly in children.

3. Convalescent hospitals in close touch with the parent hospitals for prolonged rest, supervision and education.

4. Advice as to employment.

5. The following up of the cases occurring among the children of the poor with particular reference to housing and local outbreaks. It is possible that notification of clear cases of rheumatic fever up to a definite age, for example the twentieth year, would be of much assistance to medical officers of health.

6. The careful treatment of tonsillar and other local foci.

7. Close enquiry into the influence of modern educational methods upon the incidence of chorea.

Management of the Acute Attack.—If possible a bed should be chosen of sufficient breadth to be comfortable to the patient, but sufficiently narrow to manage him with ease. For the same reason it should be of a convenient height. The sick-room should be airy, but care should be

taken to protect the patient from drafts. If there is profuse sweating the patient should be between soft blankets, but unless this is the case it is much more soothing to be between sheets, in a light flannel night-dress. The perspiration should be sponged off with a warm sponge, and the patient dried with a soft towel. It may be necessary to keep the bedclothes from the tender joints by a cradle.

While the disease is acute the diet should be fluid and mainly non-nitrogenous, for there are good reasons for believing that the renal functions are impaired. In the subacute type with carditis in children it is frequently advisable to allow as nourishing a diet as can be taken. Thirst can be quenched with lemonade, barley-water, or plain water.

Medicinal Treatment.—At the commencement of the attack the bowels should be opened. Calomel in a dose of 2 gr. (0.13 gm.) followed by a saline generally answers admirably. Severe purging is unnecessary, and if the bowels are obstinate throughout the attack cascara or senna is suitable. *Alcohol* is not as a rule required, unless for some special crisis but is useful in asthenic cases in which the tongue is dry and the prostration considerable. If the throat is affected a chlorate of potash and salicylate gargle should be employed if feasible.

Local applications to the joints are often of service. Warm cotton-wool in most cases answers all purposes, with oil of wintergreen, belladonna and opium liniment, or warm alkaline lotions. In some cases the pain in one joint may be exceedingly severe and persistent, and it is then advisable to fix it with a splint.

Of internal remedies the salts of *salicylic acid* first require consideration. Some maintain that these are true specifics, and consider that symptoms which do not yield to them are not rheumatic in nature. If this view is correct these drugs are indicated in all forms of rheumatic fever, whether articular, cardiac, pulmonary, or nervous. Experience, however, has amply shown that their effect upon cardiac rheumatism is very feeble as compared with their effect upon the arthritis and in explanation of this two reasons are advanced that the drugs are not sufficiently pushed, and that the patients come under treatment at too late a stage. Unfortunately the statement that the salicylates are a specific remedy is not established; and a further question arises: Can they be pushed without detriment to the patient? It is clear that if the reason for their employment is not an absolutely sound one it would be unwise to push them if they are in themselves deleterious.

In the writer's judgment large doses of sodium salicylate are often detrimental, and in cardiac rheumatism, especially, may introduce new dangers and in critical cases may turn the scale against the patient. It is a difficult question, on the other hand, to decide whether these drugs prevent cardiac complications. This can be asserted, that rheumatic manifestations—for example the nodules—may appear even when large doses are being given; and also that in spite of the widespread use of the salicylates, cardiac complications are very frequent.

The ill effects of large doses of these drugs are general depression, a small pulse sometimes irregular or slow, vomiting which may be most difficult to arrest, deafness, dizziness, buzzing in the ears, delirium, and occasionally irritation of the kidneys. The gravest and most remarkable

are respiratory disturbances. In some cases dyspnœa supervenes, with breathing like that in diabetic coma and the patient may collapse and die within twelve hours. These dangerous symptoms or severe vomiting may appear after a few large doses *e. g.*, 20 gr.—to a child of eight years. There is no doubt that sodium salicylate is, in large and continuous doses, essentially a depressant. The reader will understand that this opinion is neither original nor universally accepted. It is worth considering whether the depression of temperature produced by these drugs may not sometimes mislead us into a sense of false security.

The effect on the arthritis is much more encouraging, and in very many cases the salts of salicylic acid answer admirably. The treatment is more easily borne if the bowels are first opened and the particular manner in which the drug is administered will vary with the patient. To a strong adult, 20 gr (1.3 gm.) of sodium salicylate can be given with 20 gr. of bicarbonate of soda and 20 minims of tincture of ginger, in 1 oz. of chloroform-water every three hours for four doses, then every four hours, later every six hours, and lastly three times a day. When there is much distress and insomnia it is advisable to give a sedative in the evening. A patient with a feeble circulation will bear the treatment better if the aromatic spirit of ammonia is combined in 15 to 20 minim (1 cc.) doses, or 5 minim doses of tincture of nux vomica. Salicin is advisable for the delicate, and especially for delicate children.

When the temperature has fallen it is advisable to give salicylates in diminishing doses for at least a fortnight, rather than to stop them abruptly. This is a general rule; the physician will be guided by warning pains and by the temperature chart during this stage. A useful combination, after the disease is controlled, is salicylate of quinine; and from this during convalescence a change can be made to quinine, which can be prescribed for the adult in an effervescing solution.

Lutembacher, an earnest advocate of the use of salicylates, dwells on the increasing stubbornness of the disease in reacting to them when the attacks are recurrent. He has obtained good results with the intravenous use of sodium salicylate (1–30). giving 45 gr. (3 gm.) twice a day. Recently Hanzlik, Scott and others have advocated the use of cinchophen (atophan, tolysin) which is phenylcinchoninic acid.

It is claimed to produce complete relief of pain in doses reaching 150 gr. (10 gm.) *per diem* and to be free of the dangers of salicylate poisoning. This drug can be given in 30 gr. (2 gm.) doses every two hours for three doses and then every four hours. The great present need is a drug so specific as to control the heart disease but, as yet, there is no evidence to show that tolysin can achieve this.

The *alkaline* treatment has been superseded by the salicylates, although some physicians find good from full doses of potassium citrate with potassium bicarbonate.

If the heart is not damaged and the course of the illness has been favorable the patient may be convalescent in three weeks. Relapses or recrudescences are, however, frequent, and a too liberal diet or too early return to active movement is generally blamed for them. It is, however, doubtful if a careful increase in the diet can be responsible for their recurrence. Active movement is more probably a factor, for there

appears to be a decided tendency for all rheumatic manifestations to gain ground if adequate rest is not given.

It is useful to have the affected joints and limbs massaged and exercised by passive movements before voluntary movements of any considerable extent are undertaken. At this stage a stimulating liniment is also helpful. In convalescence hydropathic treatment is of service, but it is doubtful whether there is any special virtue in the waters in the locality. The systematic stimulation of the joints is most valuable when the disease is dying down and yet recovery is slow.

The inflammation may persist in one or two of the joints. Salicylates have no influence over this condition, and the erroneous diagnosis of a gonorrhœal arthritis is sometimes made. If the joint is opened, clear or blood-stained fluid exudes from the connective tissues and cavity. In the acute stage the joint should be fixed by a splint, and a cast is useful if made in such a way that it can be easily removed. A generous diet and plenty of fresh air are valuable adjuncts to the treatment of this troublesome complication. An occasional blister relieves the pain and sometimes does good to the joint. As soon as light massage can be tolerated it should be employed, and later combined with gentle passive movements. Douching and skilled massage are invaluable when the patient can bear the treatment.

One joint may remain obstinately distended with fluid, and here good food, fresh air, and quinine are more successful than the salicylates. Blisters are often useful in promoting absorption. If in spite of prolonged rest and counter-irritation the joint remains distended then skilful strapping with Scott's dressing (ung. hydrargyri co.) is indicated. The strapping should be tightened from time to time, and the joint kept at complete rest. If this fails, aspiration and flushing with 1 per cent. phenol solution are valuable; after this the joint should be firmly bandaged, and if there is any suspicion of active rheumatism full doses of salicylate of soda should be given for a few days. Bier's passive congestion has been much praised by some in the treatment of the more obstinate cases of arthritis, but the results vary. Dry heat in the form of radiant heat baths has been recommended and is a valuable stimulant.

Iodide of potassium, gr. v, (gm. 0.3) with salicylate of soda, gr. xv, (gm. 1) often relieves the articular pains. This suffering is most distressing and the above combination is well worthy of trial.

The tonic treatment of the convalescent needs some care. The anemia that so often results requires iron. Arsenic is also useful, and may be given as Fowler's solution with alkalies. For children cod-liver oil is often useful, especially when they are thin. A dry inland climate is best for those of vigorous constitution. The feeble, delicate, rheumatic convalescent does better in a dry and mild climate.

Serum Therapy.—The idea of treating rheumatic fever with some curative serum suggests itself. The antistreptococcic sera are antibacterial, very uncertain, and cannot be standardized. Those who believe that the disease is an outcome of a streptococcal infection have hopes that a polyvalent serum may do good. In our present ignorance of these complex poisons and antidotes who can deny this? The believer in the specific character of rheumatism cannot deny that other microörganisms may

possibly form allied or similar toxins and must admit that such a serum may possibly do good.

Vaccine Therapy.—The present position is not satisfactory. The vaccine used by the writer in recent years can at least be claimed as one which is logically indicated if there is any logic in this form of therapy. It is made by Dr. Nabarro from streptococcal strains obtained from undoubted cases of rheumatic fever. Some seven strains are employed. The dose for a child commences at 2,000,000 to 2,500,000 and it is given once a week gradually increasing to 500,000,000. After some years of observation the writer inclines to believe that it is helpful in cases of subacute obstinate rheumatic heart disease but not in acute cases.

The treatment of *rheumatic heart disease* is too extensive a subject to be dealt with in this article, but a few points will be touched upon. The pain of pericarditis is much relieved by an ice-bag applied to the precordium. Continuous application is the most satisfactory. Unless there is painful arthritis the writer trusts to quinine, strychnine, opium, digitalis, and stimulants, rather than to the salicylates. In exceptional cases when the right heart is acutely dilated venesection is called for. Rheumatic pericarditis may be overtreated, and the patient be more harassed by measures for his relief than by the disease itself. Paracentesis should not be attempted until there is very definite proof that the symptoms are not from acute dilatation of the heart.

Rest in all forms of rheumatic heart disease is of first importance, and the guides for relinquishing it are the pulse-rate, the size of the heart, and the absence of dyspnœa on active movement.

Cerebral rheumatism with hyperpyrexia requires prompt treatment with hydrotherapy. The cerebral symptoms are a better guide than the temperature for its employment. A temperature of 105° F. is a signal of danger. A temperature of 104° with headache and vomiting is of equal significance if there are no local lesions to account for it. The bath should be given at a temperature of about 85° F. and rapidly cooled. The patient is watched with the utmost care, and the duration of the bath graduated by his strength and by the effect upon the temperature. If there is collapse he must be at once removed, rapidly dried, and wrapped in warm blankets. If his temperature falls in the bath—from 107° to 102° F., for example—the patient should be removed, for the temperature will fall to normal after the bath. Stimulants should be close at hand but depressant antipyretic drugs are not advisable. The bath may need repetition several times in a severe case. If a bath cannot be given, ice sponging and cold packs may save life.

The Management of Those Predisposed to Rheumatism.—Careful attention should be paid to the warnings of rheumatism in children of rheumatic parentage, and the throat should be promptly treated if there is tonsillitis. Among the wealthier classes the possibility of an unsuitable house or climate should be carefully considered. Such children should not be pressed at school work and evening study often does them harm. When they are thin and irritable, enforced rest in the middle of the day is advisable. Woollen or wool and silk garments should be worn next to the skin, and if an acute attack has occurred and the climate is cold and inclement, it is advisable to winter in a dry and bracing atmosphere.

CHAPTER IX

FEBRICULA—GLANDULAR FEVER—INFECTIOUS JAUNDICE —MILIARY FEVER—ROCKY MOUNTAIN SPOTTED FEVER —PSITTACOSIS — FOOT-AND-MOUTH DISEASE — MILK SICKNESS — OROYA FEVER — VERRUGA PERUVIANA — TSUTSUGAMUSHI — ONYALAI — BIG HEEL — GOUNDOU — AINHUM—GANGOSA—TRENCH FEVER.

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FEBRICULA

Synonyms.—Ephemeral Fever; Febris Herpetica; Leichteserkältungs fieber; Simple Continued Fever; Ardent Fever.

Definition.—Under the above is included a group of acute fevers characterized by a brief course of from one to several days and the absence of the diagnostic features of the specific infectious group. With increasing refinement of diagnostic methods and consequent sharper definition of diseases on an etiological basis this indefinite group has undergone a constant and gradual contraction. The older writers devoted much space to its consideration. It was only in the nineteenth century that this group was reduced to something like its present proportions. When all allowance has been made for errors in diagnosis and aberration from type in specific fevers, there yet remains a number of cases which must be classified under the above title.

Etiology.—The causative factors are varied and indefinite. It is, in fact, our ignorance of the relation of specific microörganisms or toxins to these cases which compels us to accept such a classification as the above. In general it may be said that the young are particularly affected, the great majority of cases falling in the first two decades. The changeable seasons of the year show the greatest number of cases, while sudden exposure to great heat or excessive cold is frequently the determining factor.

Individual susceptibility plays undoubtedly an important role. There are many persons whose heat-regulating mechanism seems particularly unstable and in whom slight dietary indiscretions, emotional and intellectual excitement, or bodily fatigue, may be followed by a marked rise in temperature of greater or less duration, and, so far as we can determine, entirely unassociated with any localized infection or inflammation. It is this class perhaps which furnishes the best examples of

the ephemeral fever in the stricter sense, that is, of only twenty-four to thirty-six hours' duration.

Abortive types of the acute infectious disorders are often classed as febricula in the absence of the characteristic features. Such cases are particularly frequent after epidemics of diphtheria, scarlet fever, typhoid, or measles. Here we have only the prodromata with fever of a few days' duration and rapid convalescence. In this subgroup also, in all probability, belong most of the cases of *febris herpetica* described by Continental writers as occurring sporadically and in epidemics and distinguished from other cases of febricula by the frequent or constant appearance of herpes labialis during the fastigium or defervescence. The contention of some authorities that all cases of febris herpetica are abortive pneumonia lacks substantiating evidence. The proportion of these abortive specific disorders, formerly classed ephemera, has been greatly reduced in recent years.

Some authorities maintain that rheumatic fever may occur without any localizing manifestations and in a mild and abortive form. Central and abortive pneumonia in children unquestionably swells the list.

Gastro-intestinal disturbances account for perhaps the major part of the simple fevers. The absorption of toxins in the food, or those produced by fermentation or imperfect metabolism, is not infrequently accompanied by fever. This is especially common in childhood and, where the toxin is a recurrent factor, may give rise to a more prolonged continued fever. The stomach and intestines are normally very tolerant of partly decomposed food, and in most of these cases there must be some primary disturbance, reducing the bactericidal and digestive powers to a greater or less degree. The lumbricoid fever of French authors probably belongs in this class. Noxious vapors and sewer gas are held accountable for febrile paroxysms in certain instances. Just how these act is unknown, but clinically some very acute cases follow quickly on exposure to such influences.

Tropical *heat* is apparently responsible in a large measure for the incidence of ephemera, simple continued fever, and ardent fever in the warm countries. Those alien to the soil and unacclimatized are particularly affected, and we have all gradations of severity from mild fever of one or two days to the most severe and fatal heat prostrations. The reluctance with which many Europeans living in the East relinquish the habit of eating and drinking, of dressing and exercising just as at home, makes them especially open to attacks of this character.

Pathological Anatomy.—The autopsy findings may reveal some definite lesion, such as central pneumonia, typhoid ulcers, or general septicemia, and so enable us to determine the true nature of the affection. In other cases nothing more than general congestion of the viscera, with more or less œdema and transudation into the serous cavities, can be found. There is no specific anatomical picture associated with this group.

Symptoms.—Sudden onset with chilliness or definite rigor is very common, the temperature rising quite rapidly and reaching a moderate or even high grade, 103° to 105°, F. in twenty-four hours. No definite incubation period is recognizable ordinarily, although in many instances

it may coincide with that of some prevalent epidemic. The acute onset is especially characteristic of ephemeral fever, while simple continued fever is often preceded by a period of lassitude, loss of appetite, and slight headache, followed by a slower rise of temperature and a longer course. Accompanying the fever there is often some pain in the back and limbs, restlessness, insomnia, or drowsiness. The tongue is heavily furred, the urine scanty, and constipation is the rule, or less frequently a slight diarrhœa. In children the tendency to cerebral symptoms is more marked, delirium and even convulsions being not infrequent in the first twenty-four hours. The tonsils and pharynx are sometimes slightly inflamed and there may be a slight bronchial involvement. Fugitive erythema has been observed and sudamina over the chest, back, and abdomen. Labial and nasal herpes is frequent, appearing more commonly just before or during the defervescence. French and German writers separate these cases to form a group called febris herpetica, but the multiplication of terms is hardly justifiable.

The decline in ephemera is usually rapid on the second to the fourth day, and accompanied by profuse perspiration and critical discharges from the kidneys and bowels. In other cases the decline is slow and uneventful. In contrast to influenza there is commonly little if any residual depression or prostration. In the simple continued fever the course is from six to eight or even ten to fourteen days. The temperature is not so high and shows quite marked daily excursions. It may even be remittent or intermittent. The pulse is moderately rapid, full, and strong. There is some headache and more rarely delirium. The decline is often by lysis. Many of these cases are abortive typhoid and paratyphoid infections, such as the "Florida fever" of the Southern United States.

The "ardent fever" of the tropics is a severer form, occurring in newly arrived young persons. In it the cerebral symptoms are more marked, acute delirium being common, and may be followed by coma and death about the tenth day. The majority have a well-marked crisis and recover. It is quite certain, as pointed out by Manson and others, that many cases of so-called ardent fever are fulminant malarial infections in which the mild prodromal features have been overlooked.

Diagnosis.—At the onset and during the course of the disease we usually suspect something of a graver nature, and it is only after the entire course has been reviewed and all local and specific causes have been found wanting that we arrive at a diagnosis by exclusion.

Prognosis.—The prognosis in ephemeral and simple continued fever may be said to be uniformly good. A considerable mortality, however, is attributed to ardent fever in the tropics.

Treatment.—This is essentially symptomatic. Calomel and a saline may be indicated at the beginning, with cool or cold sponge baths when the temperature is high, and an ice-bag to the head in cases of headache, delirium, or epistaxis. The drinking of water should be encouraged, and acidulated mixtures may be of benefit. Salol and phenacetine are useful when there is much pain. Restricted liquid diet is best suited to all types, with rest in bed until convalescence is established.

GLANDULAR FEVER

Synonyms.—Acute Infectious Mononucleosis; Acute Benign Lymphoblastosis; Drüsenfieber; Fièvre Ganglionaire.

Definition.—An infectious disease of children and young adults characterized by acute onset with fever, slight congestion of the tonsils and pharynx, accompanied by enlargement of the lymph nodes, especially of the neck. Enlargement of the liver and spleen is common and acute nephritis sometimes occurs. Constipation is frequent, although diarrhœa may mark the onset. The disease is infectious and occurs most frequently in localized epidemics.

The disease was first carefully described by E. Pfeiffer[1] in 1889, Park West[2] gives valuable statistics of a large epidemic with a report of 96 cases. Recently under the terms acute infectious mononucleosis and acute benign lymphoblastosis, cases have been described which resemble clinically glandular fever. Many of the reports have been of adults and the outstanding feature, apart from the lymph-node enlargement, has been an absolute and relative increase in the blood of the mononuclear, non-granular leukocytes.

Etiology and Pathology.—Glandular fever is a disease of infancy and childhood, most of the cases occurring between the first and tenth years. Adults are not as rarely affected as was formerly thought. The two sexes appear equally susceptible, Most of the cases occur in the late winter and early spring months and exposure may play some part as a determining factor. Many cases have followed other diseases, such as influenza, measles, and scarlet fever, and it is probable that lowered resistance and malnutrition are contributory causes. In a large number of instances, however, there is no history of previous disease. Enlarged tonsils and adenoids have been frequently noted in association with glandular fever. Bacteriological reports are conflicting, and no specific causal organism has been established. That the disease is infectious is hardly to be doubted. House epidemics are common and there may be many local foci in one community. The frequency of slight inflammation of the tonsils or pharynx, with some pain on swallowing and the characteristic involvement of the glands which directly drain this area, point to this region as the portal of entry. The occurrence of cervical adenitis with some inflammation of the tonsils or pharynx, and occasionally severe nephritis, has suggested to some observers that the disease was abortive scarlet fever or diphtheria. But so many of the cases have had one or both of the diseases either before or after the attack of glandular fever that this hypothesis has little to recommend it. The incubation period is unsettled. In many cases it seemed to be from seven to ten days. The number of fatal cases is so small that there have been no thorough studies of the structural changes in the glands.

Symptoms.—The onset may be sudden, with fever, headache, loss of appetite, and constipation, or in other cases preceded by two or three days of fretfulness and general malaise. The temperature elevation is

[1] *Jahr. f. Kinderheilk*, 1889, Band **29**, p. 257.
[2] *Archives of Pediatrics*, 1896, **13**, 889.

usually moderate, 101.5° to 103°, but may reach 104° F. It is commonly remittent, being highest in the evening. The pulse and respiratory rates are proportionally increased. The tongue is furred and in most instances a slight reddening or injection of the tonsils and pharynx is found. Occasionally a very slight, filmy exudate is demonstrable on one or both tonsils. Nausea and vomiting sometimes mark the initial period and constipation is present in the majority of cases. Diarrhœa may occur and was considered by Pfeiffer as related to involvement of the abdominal lymph glands. Within twenty-four to forty-eight hours after the onset, as a rule, swelling of the glands under the sternomastoid muscle is evident, although this may be delayed until the fourth or fifth day. The glands increase rapidly in size and may be as large as an olive. They are discrete, commonly firm to touch, and very sensitive. The skin over them is normal, as a rule. Torticollis and pain on swallowing frequently accompanying the swelling. Bilateral involvement is the rule. but unilateral involvement is also noted. In Pfeiffer's cases the swelling appeared first on one side and then involved the other, and the course has been similar in most other reports. Comby and Neumann, however, report unilateral swelling as characteristic of their cases.

As the glandular swelling reaches its maximum the fever declines by crisis, with occasional critical discharges from the bowels (Park West), or by lysis, while the swelling persists, disappearing slowly in the course of two to four weeks. In many instances there is a recrudescence with fever and general symptoms, with the involvement of fresh groups of glands, as axillary, inguinal, mediastinal, or mesenteric. Those first involved may also increase in size with the reinvasion. Other cases are described in which there have been several recurrences of the disease at intervals of weeks or months.

Enlargement of the spleen and liver is very common, although in some epidemics this feature is absent. The respiratory system is not affected, as a rule. Pain and tenderness in the umbilical region are associated with the involvement of the mesenteric glands in some cases. Erythema, urticarial eruptions, and herpes have been noted in a few instances. Suppuration is uncommon and yields readily to incision and drainage. Isolated instances of otitis media and parotitis have been recorded. Nephritis has been noted in a small percentage of the cases, and is the most important complication. It appears usually in the first few days of the disease and is of a hemorrhagic type. Most of the cases end in recovery; some become chronic and a few have been fatal. In case the nephritis begins late in the disease there is a recrudescence of the cervical adenitis very like that associated with post-scarlatinal nephritis.

Recent studies of the blood indicate that a *leukocytosis* of 17,000 to to 20,000 is the rule. The mononuclear non-granular leukocytes are increased and average from 70 to 85 per cent. Apart from the large and small mononuclear leukocytes similar to those seen in normal blood, a third and predominating type is found. These cells are somewhat larger than the small mononuclear cells and contain oval, kidney-shaped, slightly lobulated, and often eccentrically located nuclei without definite

nucleoli. A negative oxidase reaction differentiates these cells from myeloblasts.

Diagnosis.—It is not until the characteristic glandular involvement has become evident that the disease may be recognized. Secondary adenitis from outspoken local causes should be excluded. Thus caries or abscesses of the teeth, thrush, follicular tonsillitis, pharyngitis, otitis media, etc., may cause swelling of the glands. But in glandular fever the involvement is out of all proportion to the local signs and it is the particular group draining the tonsil which is especially involved, while in the other infections the distribution is apt to be irregular.

The slow development, persistence, and often painless character of tuberculous adenitis render it easy of recognition ordinarily. There is no doubt, however, that cases of glandular fever seen late after the febrile stage have been mistaken for tuberculosis. In such cases time and, where possible, tuberculin will clear up the difficulty. The torticollis and pain on moving the head, with very slight glandular swelling, easily overlooked, may lead to a diagnosis of meningitis at first. When a rash is present the diagnosis may be very difficult if not impossible, until the course makes it evident from the appearance of the characteristic swellings. The early development of nephritis may cause suspicion of scarlet fever. The adenitis of Hodgkin's disease, mumps, or syphilis should offer no serious difficulties.

The differentiation from acute leukemia is not difficult on clinical grounds. In acute leukemia the patient is seriously ill, the anemia is striking and purpura and hemorrhages from the mucous membranes are common. The blood examination alone may cause confusion.

Prognosis.—The prognosis is almost uniformly good. A very few fatalities are recorded, due to nephritis or endocarditis.

Treatment.—The patient should be isolated when practicable, to prevent the spread of the disease. Rest in bed is indicated, especially on account of the danger of nephritis, and should be maintained until the temperature is normal. The diet should be light and such as the patient can take readily. Water should be freely given. Antiseptic sprays and gargles may be used to advantage, with ice-bags or warm fomentations to relieve the pain in the neck. Various authors recommend antipyretics, quinine, phenacetine, etc. Tonics, fresh air, and good food are indicated in convalescence. Iron may be necessary in cases with secondary anemia.

INFECTIOUS JAUNDICE

There is considerable confusion in the literature regarding the conditions variously described as infectious jaundice, catarrhal jaundice, epidemic jaundice, benign infective jaundice, spirochetal jaundice, infectious hepatitis, Weil's disease, etc. The term, infectious jaundice, as here used includes those cases which occur frequently in epidemics, but also sporadically as the result of some unknown infection. It is to be differentiated from the infectious hemorrhagic jaundice of spirochetal origin. It is not to be confused with the outbreaks of jaundice which occur in association with some specific disease, such as yellow fever,

paratyphoid fever, malaria, etc., nor with those outbreaks of toxic jaundice which occur as a result of some industrial poisoning, such as tetrachlorethane, trinitrotoluene, etc.

Etiology and Epidemicity.—The specific causative agent has not been found. While the disease may occur sporadically, outbreaks have been observed in groups of individuals, such as a family, institution, community, etc. Blumer[1] has made a comprehensive study of infectious jaundice in the United States, where the first epidemic occurred in Norfolk, Va., in 1812. From 1812 to 1886, 11 scattered outbreaks are recorded, 9 of which occurred in the South, 1 in Pennsylvania, and 1 in New Jersey. Between 1886 and 1920, 51 outbreaks occurred in various sections of the country, excepting the Pacific Coast States. Between 1920 and 1923, 300 known outbreaks occurred, of which about 200 occurred in New York State alone during the state-wide epidemic of 1921 and 1922.

There is a well marked *seasonal* and *age* incidence. About 70 per cent. of the outbreaks occurred in the fall and winter months and about 70 per cent. of the cases occurred in children and young adults. Although the etiological agent is unknown, the method of spread is usually by direct contact. Rats and other rodents do not seem to have any direct relation to the outbreaks. The common presence of evidence of infection of the upper respiratory tract in the early stages of the disease led Blumer to suggest that the infectious virus may eventually be found in the nose and throat secretions. Others consider the infection as probably gastro-intestinal in origin. Among troops in the Dardanelles and Mesopotamia campaigns the epidemics followed diarrheal diseases, and defective sanitary conditions, contamination of food and pollution of the water supply, were considered as predisposing factors (Willcox).

Pathology.—Fatal cases are rare and necropsy records are few. Two views prevail; the older, that obstruction of the main bile duct is the result of the extension of a catarrhal duodenitis or the formation of a plug of mucus; and the more recent view of the French school (Brulé, Abrami, and others) that the lesion involves either the liver parenchyma, bile capillaries, or both. In the early fatal cases a marked duodenitis may be found with swelling of the mucous membrane of the common bile duct, cystic and hepatic ducts. Usually when death occurs it is late in the disease and the evidences of duodenitis have disappeared. The changes then found are those of liver injury. Although most observers claim that catarrhal jaundice bears no special relation to acute yellow atrophy, the increased occurrence of this disease in localities where epidemic jaundice has been present, leads one to agree with Blumer that in certain types of severe infectious jaundice, such a condition may occasionally result.

Symptoms.—These are those of a mild general infection which may be present for a few days or several weeks before the appearance of the jaundice. Malaise, slight fever, loss of appetite, vague discomfort in the upper abdomen, constipation, and mental depression may be present for several weeks before the appearance of the jaundice. In some patients

[1] *Trans. Assn. Am. Phys.*, 1923, **39**, 189.

the initial symptoms are referable to the upper respiratory tract, rhinitis, pharyngitis, tracheitis, etc., suggesting that the initial focus of infection occurred at these places. The *jaundice* is first evident as a yellowish tinge to the conjunctivæ. Later the discoloration of the skin becomes clearly evident, but it is to be recalled that examination by artificial light may fail to show it. The duration of the jaundice varies from a few days to several months, during which time occur (1) itching of the skin, (2) epistaxis, (3) slow pulse, (4) bile in the urine, (5) absence of bile from the feces (clay colored stools), although this is not invariable, (6) progressive loss of weight, and (7) enlargement of the liver and spleen. In the more severe cases an irregular fever, chilliness, and sweats may suggest malaria or a septic infection.

The blood examination, according to the studies of Jones and Minot, reveals a reduction in hemoglobin and red cells at the height of the disease. The leukocytes may be increased early in the course with a normal differential count or an increase in the polymorphonuclears, later the leukocytes drop to normal or below with a relative mononucleosis.

Diagnosis.—The presence of an outbreak may lead one to suspect the disease before the definite appearance of jaundice. The symptoms of a mild infection, the discoloration of the skin, the absence of the specific etiological factors and the clinical characteristics of the acute infectious diseases associated with jaundice, and the laboratory findings, yield the diagnosis.

Prognosis.—This is usually good. Complications are rare and recurrences are very uncommon. Recovery, however, in some cases may be quite protracted, especially in those cases associated with prostration during the course of the disease. In only 7 of 64 outbreaks studied by Blumer were there any fatalities. Practically all of the fatal cases were in young children or in pregnant women, and in the latter instance were accompanied by abortion. The clinical picture of the fatal cases resembles acute yellow atrophy of the liver.

Treatment.—Rest in bed, a light diet, mild laxatives, and an abundance of fluids are indicated. After the acute stage and when the symptoms are clearing the continuance of a restful life is seldom acceptable to the patient, but tremendously important in hastening recovery. The diet should consist of carbohydrates principally with a restriction of fats. Milk, vegetables, and fruits should predominate. Fel bovis (gr. 15; gm. 1.0) may be given after meals. Medicinal treatment is largely symptomatic. Sodium citrate has been found useful. Duodenal lavage with magnesium sulphate solution is a valuable procedure in hastening recovery. As the jaundice fades and convalescence approaches the total amount of the food, as well as the fats, may be increased.

MILIARY FEVER

Synonyms.—Sweating Sickness; Suette Miliare; Schweissfriesel.

Definition.—An acute infectious disease rarely encountered at the present time and of short duration and exceedingly variant severity. The onset is abrupt, with or without prodromata, the cardinal symptoms

being fever, excessive continuous sweating, great anxiety and oppression, with rapid and often tumultuous heart action and respiratory distress. On the third or fourth day an erythematous rash appears, accompanied by miliary vesicles and sudamina. With the appearance of the rash the fever subsides gradually and slow recovery follows, or death may ensue in a few hours to three or four days after onset. There is little reason to doubt the substantial identity of miliary fever with the "sudor anglicus" or sweating sickness which swept over England in five epidemics between 1485 and 1557.

Etiology and Pathology.—The disease appears more frequently in the spring and summer months. It appears suddenly in localized epidemics which are of very brief duration, often not more than two weeks. In this time a very large proportion of the population may be affected. All ages and both sexes are susceptible, although it is more prevalent among the robust. That the frequency is greater in women seems settled. The lethality in modern epidemics varies from 33 per cent. to zero and may be even so variable in different places during the same epidemic. There is some evidence in favor of the transmission of the malady by direct and even by indirect contagion. Cultures from the vesicles, the blood, and organs have not led to the discovery of the causative factor.

There are no striking changes in the viscera. The spleen is somewhat engorged and shows cloudy swelling. The same is true, to a less degree, of the liver and kidneys. The heart is flabby and shows marked segmentation and fragmentation. There is slight swelling of Peyer's patches and often some blood in the intestine. The nervous system shows no distinctive changes beyond hyperemia and slight increase in the cerebrospinal fluid in fulminant cases. Parrot and others made repeated attempts to inoculate healthy individuals with the contents of vesicles, but were unsuccessful.

In 1905 an epidemic of 126 cases occurred in Austria and is reported by Scholz.[1] In the following year an epidemic of 6000 cases was observed by Chantemesse[2] and others[3] in Northern France. In their study, they were led to advance the hypothesis that the disease is transmitted by fleas from field mice.

Symptoms and Course.—The disease may be preceded by a brief prodromal stage, with malaise, headache, vertigo, muscular weakness, joint pains, and dryness of the mouth, sometimes nausea and vomiting. The onset is sudden and the first symptom is sweating, although this may be preceded by a slight chill. At the same time the temperature rises and the patient feels a burning heat in the skin despite the extreme sweating.

The temperature varies with the severity of the epidemics and the individual cases. Averaging 102° to 103°, it frequently reaches 105° to 106° in severe cases, and may be even higher. The pulse-rate is increased out of proportion to the temperature and is further peculiar in its variability coincident with the cardiac paroxysms characteristic of the disease. The heart beat during these paroxysms is irregular and almost

[1] *Zeit. f. klin. Med.*, 1906, Band **54**, pp. 542–564.
[2] *Bull. Acad. med. de Paris*, 1906, 3d Serie, Tome **56**, pp. 293–296.
[3] *La clinique de Paris*, 1906, Tome **1**, pp. 435, 437, and 787–789.

delirious. The palpitations cause the patient great anxiety. Marked pulsation and a peculiar sensation of constriction in the epigastrium are among the classical symptoms. This is generally constant to a greater or less degree and increased in paroxysms of variable intensity. Associated with it there may be tenderness on pressure. A feeling of laryngeal occlusion and impending suffocation is also very common. These phenomena are subjective and of nervous origin as examination of the heart and lungs discloses no abnormality.

Other nervous features associated with the primary or sweating stage, although of less importance, are great prostration, delirium, clonic convulsions, and cramps in the hands and legs. The lips and tongue are dry, the breath foul, and there is marked anorexia with great thirst. Often nausea is present and less commonly vomiting. The urine is greatly reduced in volume and temporary anuria is often observed. The low output persists until the sweats cease, when there is often a sudden critical discharge of urine rich in salts. Albuminuria is not common. There is no leukocytosis. Epistaxis and hemorrhages from the bowel occur frequently in some epidemics, although the bleeding is rarely serious. The rash may have a purpuric character in such cases. There is commonly moderate enlargement of the spleen with little or no increase in the size of the liver.

The *sweating* is the most striking and persistent feature of the disease. It is extraordinary great in amount and differs from the sweating of most febrile diseases in appearing with the onset of fever, continuing during the fever, and increasing with increase of temperature. It is probably due to toxic excitation of the medullary centres.

The *eruption* appears on the third or fourth day and is seen first on the neck and back, under the breasts and axillæ, and between the thighs. A general erythema is present, in addition to which appear (*a*) sudamina (miliaria alba or crystallina), (*b*) red papules becoming vesicular (miliaria rubra), (*c*) petechiæ of variable size (purpura miliaria). The appearance of the eruption is preceded by itching. The red papulo-vesicular type is most frequently observed, with usually some sudamina; the purpuric type is not seen so often and occurs in the cases with other hemorrhagic manifestations. Vesicles are also frequently found on the mucous membranes of the conjunctiva, nose, and mouth. The rash may come out rapidly and cover the whole body in twenty-four hours or slowly and in successive crops. Thus desquamation may be advanced in the regions first affected, while other areas show the early stages.

The eruption stage marks a crisis and the symptoms above noted usually abate gradually after its appearance. The fever drops with a rapidity proportionate to the development of the rash. The nervous and digestive disturbances become less marked and the sweating more slowly lessens, disappearing only with convalescence.

Convalescence is very slow in mild as well as in severe cases. There is usually great weakness and anemia and loss of weight. Tremor, cardiac arrhythmia, insomnia, and general nervousness are apt to persist for some time and months may elapse before the patient is fully restored.

While the course is usually favorable, it is not always so. In the

fulminant cases death may ensue within forty-eight hours from the onset. In such cases extreme hyperpyrexia, dyspnœa, and very rapid pulse, with precordial pain and constriction, are characteristic. Delirium and death from suffocation end the attack often before the rash has appeared. In other cases which begin mildly a similar development may take place suddenly on the third or fourth day before the appearance of the rash. More rarely sudden collapse occurs, with cyanosis and death in a few minutes.

In the second stage there is occasionally death following multiple hemorrhages from the nose and intestinal tract. Recrudescence is sometimes observed during the second stage, accompanied by intensification of the fever, sweating, and nervous symptoms. Relapses are extremely common in the first two weeks, and are usually milder than the primary attack.

Diagnosis.—This is not difficult with typical cases. The abrupt onset, sweating with fever, nervous phenomena, and the vesicular rash are peculiar to this malady. Very mild and atypical cases may be confused with measles.

Prophylaxis and Treatment.—As the evidence points to the possible infectious character of the disease, patients should be isolated and rigid disinfection of house and clothing enforced. The therapy is symptomatic. The patient should be lightly covered and the room thoroughly ventilated. The wet clothes should be frequently changed. Cold packs give much relief during the hyperpyrexia and diminish the nervous symptoms. The diet should be bland and mostly liquid, with large amounts of water. In serious cases the symptoms must be met as they arise. Atropine in guarded doses may be helpful in cases of excessive sweating and anuria. Grave nervous phenomena and cardiac delirium are best met by the careful administration of morphine. The efficacy of quinine is very doubtful. Careful dieting and the use of iron and tonics aid complete restoration during convalescence.

ROCKY MOUNTAIN SPOTTED FEVER

Synonyms. Tick Fever of the Rocky Mountains; Piroplasmosis Hominis; Black Fever; Blue Disease.

Definition.—An acute infectious disease of man characterized by sudden onset, with chill, continued fever, headache, severe pains in joints and bones, and a macular eruption, becoming petechial, which appears first on the ankles and wrists, later spreading all over the body. The disease known as "spotted fever" has been observed in the Bitter Root Valley since the early days of permanent occupation by white settlers, the first recorded cases occurring at Woodside, Montana, in 1873.

The disease is endemic in the Bitter Root Valley of Montana, appearing in the spring months, and occurs also in the neighboring mountainous parts of Idaho, Wyoming, and Nevada. It affects all ages and both sexes. The mortality varies with location and from year to year, averaging 70 per cent. in Montana and from 1 to 3 per cent. in Idaho. The specific infectious agent is probably bacterial in nature and to it Wolbach has

given the name *Dermacentroxenus rickettsii*. It can be conveyed by the bite of the "wood tick," *Dermacentor andersonii* (Stiles) and is transmissible experimentally to monkeys, guinea-pigs, and rabbits.

Etiology and Pathology.—The incidence is striking as to localization and time of appearance. It occurs only in the high valleys of the circumscribed mountain regions above noted and in the spring and summer months, the cases appearing as early as March and as late as July, but the greater number in the months of May and June. All ages and both sexes are susceptible, but the incidence is greater in males between the ages of twenty and forty years and among those whose occupation leads them afield and into the forests; cattlemen, farmers, lumbermen, and miners are most apt to be affected. The cases appear singly in widely separated places and there is little or no evidence to point to family or house infection.

The first pathological study of the disease was made by Wilson and Chowning.[1] They described bodies in the blood which they held to be hematozoa and named *Pyroplasma* (*Piroplasma*) *hominis*. Subsequent investigation, however, by Stiles, King, Ashburn, Ricketts, and others failed to substantiate the findings. The virus is not filterable and probably bacterial in nature. Bacteria resembling the rickettsia group of organisms have been found in infected ticks and in the endothelial cells of the bloodvessels of guinea-pigs (Wolbach); in man and in eggs of infected ticks (Ricketts); in the red cells of patients and infected guinea-pigs, as well as extracellularly (Frick). Wolbach has named the microorganism, *Dermacentroxenus rickettsii*. Wilson and Chowning first suggested the role of the tick in conveying the disease. Stiles[2] (1905) published a zoölogical study of the disease and a complete bibliography.

In 1906, Ricketts,[3] succeeded in transmitting the disease to guinea-pigs and monkeys by intraperitoneal injection of the blood of patients suffering from spotted fever, and finally established a constant transmission in laboratory animals. Experimental animals, surviving one attack of the disease, show a high degree of immunity to further inoculation.

King[4] and Ricketts[5] separately demonstrated beyond doubt that the ticks, *Dermacentor andersonii* (Stiles), male and female, are capable of transmitting the infection by their bites. These ticks appear with the first warm days of spring and begin to disappear in June. They live on the domestic animals of the region and secure the infection through feeding on rodents, such as ground squirrels, chipmunks, mountain rats, etc., which act as reservoirs of the disease. The virus is transmitted by the saliva of the tick. A tick once infected continues so for the remainder of its life.

The *pathological* findings include as the main feature extensive petechial

[1] *Jour. Am. Med. Assn.*, 1902, **39**, 131–138.

[2] *Bulletin No.* 20, *Hygienic Laboratory of United States Public Health and Marine Hospital Service.*

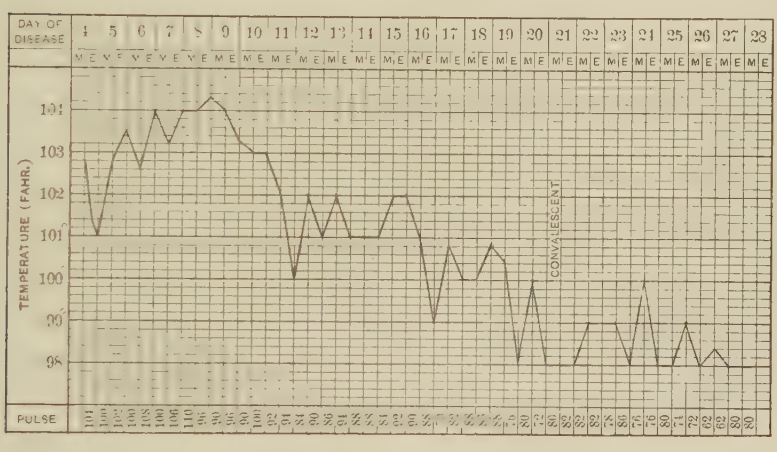
[3] *Jour. Am. Med. Assn.*, 1906, **47**, 33–36.

[4] *Public Health Reports*, July 27, 1906.

[5] *Jour. Am. Med. Assn.*, 1906, **47**, 358 and 1067–1069; Carpenter Lecture, *Med. Rec.*, New York, 1909, **76**, 842, also *Ricketts' Memorial Volume*, University of Chicago, 1911.

involvement of the skin, confluent over dependent areas, and most abundant on the arms, legs, and back. The capillaries of the skin are engorged and there is some extravasation of blood in the rete mucosum. Evidence of recent tick bites is reported in a number of cases. The cerebral and spinal meninges are normal or show slight hypostatic congestion. No meningitis was found in any case. The lungs are normal or with hypostatic congestion; the heart flabby and friable, with small petechiæ under the epicardium. The stomach and intestines are normal. The spleen is greatly enlarged, dark in color, and diffluent, the Malpighian bodies obliterated, and there are many phagocytic leukocytes with red blood cells, but no free pigment. The liver is enlarged and shows extensive fatty infiltration; the pancreas is also increased in size. The kidneys are large and red with small hemorrhages under the capsule and in the pelvis. The cortex is swollen and congested, but not adherent; the pyramids red and sharply defined; general cloudy swelling is evident microscopically. Gangrene of the prepuce and scrotum is not uncommon.

Fig. 26


DAY OF DISEASE
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E
TEMPERATURE (FAHR.)
101
103
102
101
100
99
98
CONVALESCENT
PULSE

Rocky mountain spotted fever. Temperature curve. (Wilson and Chowning.)

Symptoms and Course.—The incubation period is from three to ten days and during this time there is increasing malaise, with pain in the bones and muscles. There is ordinarily a severe chill at onset which may recur. Nausea and headache are common. The bowels are constipated and pains in the limbs are characteristic. The tongue is furred and there is a yellowish tinge to the conjunctivæ, with deepening jaundice during the course. Nose bleed is not infrequent at onset and may be severe in the second week. The temperature rises rapidly after the chill and is continuous, with but slight daily variations. It usually reaches 103° to 104° on the second day and may continue to rise in the following week and, in fatal cases, be as high as 105° to 107° F. In the milder cases the temperature declines slowly after the tenth to the twelfth day and reaches normal during the third week.

The pulse is characteristically very rapid, ranging from 110 to 140 in average cases and much higher in very severe ones. At first full and strong it becomes thready as the disease progresses. The respiratory rate is also increased, averaging 36 or more per minute. Slight bronchitis is common and pneumonia is a well-recognized complication.

The blood shows a steady diminution of red cells and hemoglobin during the fastigium and defervescence with regeneration after the temperature falls. The leukocytes are normal or moderately increased.

The digestive system may show little or no disturbance during the early part of the disease, but nausea and vomiting are apt to appear in the second week and may be persistent and excessive in fatal cases. Enlargement and tenderness of the spleen are marked and appear early. The liver is also palpable just below the costal border. There is no general abdominal tenderness, as a rule. Hemorrhages from the nose, mouth, stomach, and bowels are not uncommon. Bloody effusions into the joints are also reported. The urine is scanty and high colored, with a trace of albumin and hyaline, epithelial, granular, and blood casts, but hemoglobinuria is absent.

Restlessness, irritability, pain and hyperesthesia with photophobia are common nervous symptoms. In severe cases stupor with low delirium is frequent and coma usually precedes death. Slight opisthotonos is reported for a few cases, but muscular rigidity and Kernig's sign are absent. Convulsions have been noted rarely in children.

The *rash* appears on the second to the seventh day after onset, most commonly on the third day. It is first seen on the wrists and ankles, spreading toward the trunk, and is found on the forehead and breast, but especially thick over the back. The abdomen shows fewer spots and is involved later. In severe cases the palmar surfaces of the hands and feet and also the scalp may be thickly covered with the eruption. At their first appearance the spots are bright red, disappear on pressure, and vary from 1 to 6 mm. in diameter. These macules become steadily darker and definitely petechial. By the seventh to the tenth day they have usually reached the fullest development when the fever is also at its height. At the same time icterus is marked and the spots may be confluent over dependent parts, giving a mottled appearance.

With the decline of the fever the spots fade, leaving a stain in the skin. Exacerbations or sweating may cause them to reappear and during convalescence a warm bath or exercise will bring them out. Often in severe cases there is gangrene of the skin over the toes, fingers, elbows, ears, and frequently scrotum and penis. Œdema is also noted over the head, face, and dependent parts. Desquamation begins when convalescence is well advanced and is general, although most marked, on the hands, feet, and face. Convalescence usually begins about the fourth week and is generally slow. In a very few cases relapses have been noted. The principal complications are gangrene, above noted, and lobar pneumonia. Immunity is conferred by one attack.

Diagnosis.—To those who have seen the disease its recognition is easy. Its endemic and seasonal occurrence, the character of the rash and associated pain and nervous phenomena are sharply defined. From

typhus fever it is distinguished by its occurrence in isolated cases in scattered communities and the general characteristics. The onset in typhus is abrupt and the decline by crisis. In typhoid fever the lower fever, slow pulse, diarrhœa, Widal test, and positive blood cultures make the distinction easy. In cerebrospinal meningitis, the greater prevalence in children, frequent absence of rash, more intense nervous symptoms, and the demonstration of the organism by lumbar puncture render the differentiation fairly easy. A mild type without any rash is said to exist. Its diagnosis is, however, not at all clear.

Prognosis.—While delirium and marked nervous features are considered unfavorable, little can be premised from the severity of the eruption or the height of the fever. Death occurs most frequently between the sixth and twelfth days and patients surviving the second week are likely to recover. The mortality is greater among the old and less in children.

Prophylaxis.—This is directed toward the destruction of ticks and the reservoirs of the virus. Sheep, horses, and cattle which act as hosts for the tick should be dipped and scoured. Rodents should be destroyed. In man, after exposure, search for ticks which require at least one or more hours to become attached and feed, and their removal with cleansing tends to prevent infection.

Treatment. There is no specific remedy and the therapy is symptomatic. Good surroundings with careful nursing are important. The patient should be protected from noise and have the room darkened. The diet should be liquid or soft in character until the decline of the fever. Sponge baths are helpful in reducing the nervous phenomena and lowering temperature. Phenacetine and other antipyretics are in common use. Free purgation with calomel and saline cathartics, supplemented by enemata when necessary, is recommended by most observers. Morphine may be necessary for the relief of excessive pain. The forcing of water and use of diuretics are indicated and saline infusions may be necessary in severe cases. Sodium citrate is recommended by Michie and Parsons. The efficacy of quinine is not settled, the opinions being widely divergent.

PSITTACOSIS

Definition.—An epidemic disease of parrots distinguished by general debility, loss of appetite, and chronic enteritis, with a high mortality. The same name is also applied to a disease in man characterized by an onset like typhoid fever, with signs of severe atypical pneumonia. This has occurred in house epidemics and been ascribed to infection from sick parrots.

Etiology and Pathology.—The first recorded epidemic was in 1879 (Ritter[1]) and since then epidemics have been reported from Germany, France, Italy, England,[2] and America. In the Paris epidemic of 1893, Nocard isolated the specific bacillus, *Bacillus psittacosis*, from the bone-marrow of parrots dead of psittacosis and showed that it was very patho-

[1] *Deut. Arch. f. klin. Med.*, 1879, **25**, 53.
[2] Gulland: *Brit. Med. Jour.*, 1924, ii, 309.

genic for parrots, pigeons, fowls, and laboratory animals. In 1896, Gilbert and Fournier isolated *Bacillus psittacosis* from human beings as well as parrots. Perry[1] has studied the close relationship between *Bacillus psittacosis* and the Salmonella group of organisms, *Bacillus enteritidis* (Gaertner), *Bacillus paratyphosus* and *Bacillus aertrycke*. Numerous observers, however, have failed to find the specific bacillus in man, and cultures have yielded the pneumococcus, streptococcus, colon bacillus, and other organisms. Nocard advanced the theory that the bacillus of psittacosis prepared the way for secondary pneumococcus infection, and this view is generally held by the French observers. The pathological findings in parrots show enteritis with cloudy swelling of the liver, spleen, and kidneys, but no pulmonary involvement. In man the principal feature of the fatal cases has been the presence of pneumonia with signs of a general infection.

The possibility that this disease may be transmitted from parrots to man cannot be denied when the incidence in relation to the sick parrots and the simultaneous infection of whole families are taken into consideration. The bacteriological findings are very contradictory and unconvincing. Exactly similar house epidemics of atypical pneumonia have been recorded entirely unrelated to the disease in parrots.

Symptoms and Course.—The malady resembles typhoid fever complicated with pneumonia. The incubation period is uncertain, varying from seven to twenty-five days in different reports. Dubief gives the average as seven to ten days. The onset is variable: in some cases sudden, with chill, as in pneumonia; in others gradual, with headache, malaise, photophobia, loss of appetite, nausea, constipation, great lassitude, and weakness. In those who practise mouth-to-mouth feeding of parrots the initial involvement may be a diphtheroid stomatitis, with enlargement of the submaxillary glands.

The rise of temperature is usually rather rapid, reaching 102° to 104°. The fever is continuous with daily remissions. The pulse varies from 100 to 120. From the first there is cough, mucopurulent or bloody sputum, and increased respiratory rate. On auscultation, fine moist rales are heard throughout both lungs. There is usually no evidence of consolidation at the time of onset. The tongue is dry and furred and the breath foul. Abdominal symptoms are not marked. The spleen is, however, enlarged and, rarely, scattered rose spots or petechiæ are seen. Diarrhœa or constipation may be present, the former being more common. Nausea and vomiting are not usual except at the onset. The patient is dull and stupid, with more or less marked delirium. In uncomplicated cases the duration is fifteen to twenty days and the prognosis is generally favorable. With pneumonic symptoms the aspect is graver, and to this factor the high mortality is due. The pneumonia may be lobar or lobular and involve different areas in succession.

Diagnosis.—The recognition of the disease is difficult, and depends principally on the association of house epidemics with the presence of diseased parrots. The clinical picture is much like atypical pneumonia.

[1] *Brit. Jour. Exper. Path.*, 1920, **1**, 131.

Severe influenza has many points of similarity and the first Paris cases were so diagnosed by Dujardin-Beaumetz.

Prognosis.—The average mortality is between 35 and 40 per cent., being highest in old people and notably less in children.

Treatment.—In view of the possible agency of the parrot in conveying this infection the handling of sick birds should be discouraged. Cleanliness and disinfection of the cages should be carefully observed. The patients should be isolated as a precautionary measure. Tub baths and cold packs are highly recommended by the French observers, who treat the cases throughout like typhoid fever.

FOOT-AND-MOUTH DISEASE

Synonyms.—Aphthæ Epizoöticæ; Aphthous Fever; Maul und Klauenseuche; Fièvre Aptheuse.

Definition.—An infectious disease of cattle and other domestic animals, the characteristic features of which are moderate fever, disappearing with the development of a vesicular eruption on the mucous membranes of the mouth and on the skin above the hoofs and between the toes. Ulceration follows, with salivation and great tenderness of the affected parts. Loss of appetite and great emaciation accompany this stage. Healing is slow, but most animals recover. Fatal apoplexy is not uncommon and death from septic infection of the sores is also well known.

The malady is transmissible to man through unboiled milk or butter and cheese, and also directly from the saliva or contents of the vesicles of infected animals gaining entrance through abrasions of the skin. It is especially frequent in children and in those whose work brings them in contact with diseased cattle.

The aphthous epizoötic was first described in human beings in the eighteenth century. Epizoötics have been frequent and entailed great losses throughout Italy, Germany, France and Switzerland. In England, where the disease first made its appearance in 1836, serious outbreaks have occurred in 1883, 1884, 1892 and during the past five years. In America the disease has never been widely prevalent. Local outbreaks have been recorded in New England and the Middle States in 1870, 1884, and 1903, and in Pennsylvania in 1908. Human infection has constantly accompanied the epizoötics, and its incidence is probably much greater than the reports indicate, as the milder cases were not seen.

There is a marked variation in the virulence of the disease as it affects animals and in its infectivity for man. In the recent epidemics in Britain the mortality among animals and the infectivity to man was very low. In Continental outbreaks, however, animal mortality has varied from 2 to 50 per cent. with a corresponding rise in the number of human cases. Petit records the occurrence of 20 cases among 300 inhabitants of a Luxemburg village, occurring five days after the outbreak was discovered in the animals of that locality.[1]

Etiology and Pathology.—The specific organism is still unknown despite the great amount of work devoted to its discovery. Bacilli,

[1] Cameron: *Lancet*, 1922, i, 353, also Ministry of Health Circular, *Lancet*, 1922, i, 1014.

cocci, streptothrices and protozoa have been described by different observers as the causative factor. In 1898, Loeffler and Frosch[1] demonstrated that the virus was ultramicroscopic and passed through the finest porcelain filters. The filtered lymph, free from all demonstrable bacteria, was capable of producing the typical lesions in all the animals susceptible to natural infection and transmissible indefinitely from them to others. This discovery discredits absolutely all the findings of organisms of whatever sort.

The infection is spread readily by contact with sick animals or by the dung or liter or the use of stalls or drinking troughs previously used by them. It is also communicable from one species of animal to another; cattle, horses, sheep, goats, swine, deer, and even dogs and fowls are susceptible. The demonstration by Mohler and Rosenau[2] that the 1908 outbreak was due to the importation of contaminated vaccine is of great interest and importance.

The portals of entry for natural infection are not clearly established, but animals may be infected by injection of lymph from the vesicles into the blood, peritoneal cavity, muscles, and digestive tract, or by rubbing on the scarified mucosa of the mouth. Cutaneous and subcutaneous infection is irregular and uncertain. Two to three weeks after the beginning of the attack most animals show a greater or less degree of natural immunity, which is, however, of uncertain duration. An antibody capable of protecting against a certain amount of virus is present in the serum during this time. This immunity can be greatly increased in heifers and young swine by repeated injection of virus in increasing doses, and a protective serum conveying a brief passive immunity to other animals has been made (Loeffler and Uhlenhuth). Active immunization has not been successfully carried out.

Of the typical morbid anatomy, apart from complications, little is known, as few animals die from this cause directly. The vesicles form in the rete mucosum and the subsequent ulceration is usually completely healed without scar by extensions of the epithelium over it. Animals dying during the disease have shown vesicles in the œsophagus, trachea, and bronchi. The ulcers on the feet are especially liable to secondary infection, which may lead to severe inflammation of the matrix and separation of the hoof, arthritis, bone necrosis, and pyemia.

Symptoms and Course.—In man the disease sets in with fever after variable incubation periods of two to ten days. The fever is usually not very high, but may reach 104° F. and be accompanied by a shaking chill. Loss of appetite, languor, pains in the muscles, back, and head, with cramp-like pains in the abdomen, nausea, and vomiting are common.

The primary seat of infection in man is most frequently the *mouth*, due to drinking infected milk. The mouth feels hot and dry and there are areas of hyperemia over the lips, base of the gums, margin of tongue, and mucosa of the cheeks. The vesicles form about two to three days after the initial symptoms and are at first small and discrete, but tend to enlarge rapidly and become confluent. They may extend over the

[1] *Centralbl. f. Bakt. u. Parasit.*, 1898, Band **23**, abt. i, pp. 371–391 u. ff.
[2] *Bureau of Animal Industry Circular* 147, 1909.

whole buccal mucosa and into the pharynx, larynx, œsophagus, and trachea. On the skin the blebs are often found about the mouth and nose. The conjunctiva and cornea may be involved and the skin between the toes and fingers is frequently affected. Among those working with sick cattle the borders of the nails are often attacked and severe panaritium may follow with secondary pyogenic infection. In severe cases the vesicles may be distributed over the whole body, especially about the breasts, thighs, gluteal folds, and genitalia.

With the development of the vesicles the temperature falls. At the same time the tongue and lips swell and there is difficulty and pain in swallowing with marked salivation. There may be also a profuse nasal discharge. The content of the vesicles is at first clear, but soon becomes purulent and invaded by the mouth bacteria. The vesicles are easily broken and leave weeping, shallow ulcers, which are very painful when touched. This painful ulceration of the mouth and gullet often leads to serious inanition through the refusal of food. Speech may also be difficult. The submaxillary and sublingual lymphatics and occasionally the salivary glands may be swollen and painful. In the vesicular stage there is often colic and diarrhœa or bloody stools in children.

The course of the disease when uncomplicated is generally mild and favorable. The ulcers become crusted over and gradually covered with new epithelium, leaving no scars except where there has been pyogenic invasion of the corium and subcutaneous tissue. The average duration is two weeks from the onset, although very mild cases may be well in less time and more severe ones last six to eight weeks. In young children the danger is greater from the severe disturbance of nutrition, rendering them liable to severe gastro-enteritis and even death from inanition.

Diagnosis.—In any case of aphthous disease the history should be carefully noted, with special reference to the presence of foot-and-mouth disease in the neighborhood or at the source of milk and butter supply. These facts with the characteristic onset and the superficial rapidly developing vesicles would make the diagnosis certain. The common aphthæ in children are small, round, yellowish, discrete, and unaccompanied by acute general symptoms. Stomatitis ulcerosa is distinguished by the extensive and deep infiltration and rapid necrosis, especially of the gums. Inoculation of the contents of the vesicles into the mouths of sheep or swine would make the diagnosis definite. The hands may be the primary seat of the vesicles in those who work with cattle.

Treatment.—Prophylaxis is of primary importance. Isolation and slaughter of infected herds and condemnation of the dairy products, with thorough disinfection of the stalls and troughs should be enforced. The milk is rendered innocuous by heating to boiling. But milk from sick cattle should not be used, even if it be sterilized. The injection of bichloride of mercury has been recommended by Baccelli for the treatment of cattle and widely used in Italy. The German commission reported adversely on the Baccelli treatment, and think it may be harmful. It is not applicable to man.

In man it is well to isolate the patient and apply local remedies to the ulcers. Chlorate and permanganate of potassium are recommended

as mouth washes and the ulcers may be touched with silver nitrate or copper sulphate. Drying powders may be applied to the external lesions. In severe cases or in young children, feeding by nasal or stomach tube or nutritive enemata may be indicated.

MILK SICKNESS

Synonyms.—Trembles; Slows; Puking Fever.

Definition.—A disease primarily of herbivorous animals and transmissible to man or other animals feeding upon the milk or flesh of infected individuals. The disease is characterized by gradual loss of appetite, obstinate constipation, drowsiness, muscular tremor, and convulsions; or it may be latent and develop fulminantly in such cases by forcing the animal to vigorous muscular exertion.

This remarkable disease is known only in certain widely scattered districts of the United States, including the upper and middle parts of the Mississippi Valley, the mountain regions of the Southern States and the Southwest. The report of Jordan and Harris[1] gives the history and literature.

Etiology and Pathology.—The disease is not confined to any time of year, but is more prevalent in the summer and fall, and apt to be more severe in dry years. The infected pastures are never increased in area, but seem rather to decrease with time. Areas formerly free have not been known to become infected. Clearing and cultivation, if persisted in, render the pastures safe. Jordan and Harris isolated an organism, *Bacillus lactimorbis*, from the milk and tissues of infected animals. Clay was unable to demonstrate this organism in milk. He considers the disease as an intoxication from the alkaloid or active principle of *Eupatorium ageratoides*, a plant which grows in thickly wooded pastures near sandy bottom streams. Herbiverous animals seeking the wooded pastures during the dry season when the heat is intense and the grass gone, eat freely of the poisonous plant, Cattle are principally affected and the disease is transmitted to man by the milk and meat.

The pathological findings in cattle or in animals secondarily infected are the same: some injection with great contraction of the intestines and stomach, enlargement and softening of the liver and spleen, while hemorrhages and exudation into the serous cavities are constant. There is often great engorgement of the cerebral vessels, with fibrinous exudation on the meninges and softening of the brain.

Symptoms.—In man the disease comes on after an incubation period of three to ten days, with languor, loss of appetite, and extreme constipation. Headache, tinnitus aurium, and muscular pains may be present in some epidemics and absent in others. There is great thirst, with nausea and persistent vomiting. In severe cases the vomitus is of a bile-tinged and soapy character and may contain blood. The tongue is swollen, flabby, shows the impress of the teeth, or may be protruded from the mouth and coated with a whitish fur. The breath has a peculiar,

[1] *Jour. Infect. Dis.*, 1909, **4**, 401.

sweetish odor, which is quite characteristic. The pulse is quick, full, and soft, and there is no fever or only a very slight rise of temperature. The cerebral symptoms may be varied. Great irritability, convulsions, and marked delirium are characteristic of some epidemics, while in others drowsiness and coma are more common. The abdomen may be moderately distended and is doughy on palpation, and there is often marked epigastric pulsation. The urine is scanty, pale, and commonly shows a trace of albumin. The leukocyte and differential counts are normal. In fatal cases death may occur in from three to ten days after the initial symptoms, coma and gradual cardiac failure being the terminal features.

The mortality varies greatly in different epidemics and may be from 10 to 90 per cent. The milder cases show a slow abatement of the symptoms, sometimes with critical discharges and a long convalescence. In this stage the slightest muscular exertion may bring on typical "trembles," as seen in cattle. Very often the patient is unable to work for months; others are more or less permanently incapacitated. Progressive dementia is said to have followed severe attacks.

Diagnosis.—In regions where "trembles" in cattle is prevalent, the recognition offers little difficulty, and in any case the occurrence of the characteristic nausea and vomiting, great thirst, enlarged tongue, and obstinate constipation without fever would make the diagnosis probable and lead to a careful investigation of the milk, butter, and meat supply. Cases are apt to occur simultaneously in families. Occasionally severe gastro-enteritis or typhoid fever may be mistaken for milk sickness in regions where this prevails. The history and course should soon lead to a correct diagnosis.

Treatment.—Absolute rest and free purgation, preferably with salines or castor oil, persistently administered until effective, give excellent results. The free use of alcohol as an antidote is advised by Clay. Stimulation is indicated in most cases. During convalescence strychnine and iron are advised. The patient must avoid severe muscular exertion for a long time lest he precipitate an attack of "trembles."

OROYA FEVER[1]

This acute infectious disease is endemic in the valleys of the west side of the Andes at elevations of from 3000 to 9000 feet, and occurs chiefly during the months from January to April. The causative agent is the *Bartonella bacilliformis*, an organism intermediate between bacteria and protozoa. An insect transmitter is suspected but not yet known. After an incubation period of about three weeks the disease sets in insidiously with malaise, weakness, headaches, pains in the bones and joints, irregular fever, and a rapidly developing *severe anemia*. The spleen, liver and lymphatic glands are somewhat enlarged and tender. The blood exami-

[1] Previous to the work of the Harvard Commission under Strong in 1915, oroya fever and verruga peruviana were considered to be the initial and later stages of one disease. Since they are endemic in the same locality, they may coëxist. Their independence, however, has been demonstrated by Strong and his colleagues.

nation reveals the severe anemia and in some instances the causal organism. A leukocytosis is present. Death from the severe anemia results in 20 to 40 per cent. of the cases in two to three weeks. A terminal delirium is common. The *treatment* is symptomatic. Arsphenamine has been reported upon favorably by some observers.

VERRUGA PERUVIANA

This chronic infectious eruptive disease of unknown etiology is endemic in certain valleys of the Andes in Peru. Strong and his associates were successful in inoculating animals. The disease is characterized clinically by an incubation period of from two to six weeks which is followed by a febrile disturbance with pains in the joints and an eruption. The *eruption* may consist of numerous small raised, pinkish papules which later become darker in color and nodular in character (the miliary type); or larger less numerous and slowly developing nodular masses which may ulcerate and bleed or become strangulated (the nodular type). The face, neck, and limbs are the favorite sites, although the whole body may be involved. The smaller lesions involve the mucous membranes, as well as the skin. The larger lesions are found principally about the knees and elbows. The eruption tends to recur in successive crops and the disease may last two or three months, or longer. The mortality is from 10 to 30 per cent. *Treatment* is symptomatic. Local ulcerations require careful cleansing and protection. The larger masses may require excision. Small doses of arsphenamine intravenously have been tried with benefit (Manson-Bahr).

TSUTSUGAMUSHI[1]

This acute febrile disease, also known as shimamushi, Japanese river fever and flood fever, occurs chiefly along the river banks of the western part of the Island of Nippon and also in Formosa and possibly Korea. The cause is not definitely known, but the virus is spread by a mite, the *Trombidium akamushi*, which feeds on field mice. A pathogenic microorganism of the Rickettsia group has been isolated from experimentally infected animals by Sellards[2] and provisionally named *Rickettsia nipponica*. The disease occurs in the summer months among those engaged in harvesting and handling hemp. The bite of the infected mite gives rise to a small ulcer most commonly located in the arm pit or about the genitals. After an incubation period of five to twelve days chilliness or a severe rigor is followed by a sudden rise of temperature with fever symptoms, lymphangitis, enlargement of the regional glands, and an exanthem. Conjunctivitis and bronchitis are present and the spleen is usually enlarged. The *eruption* is macular in character and appears about the seventh day on the face and spreads to the rest of the body. It disappears in four or

[1] There are four diseases—typhus fever, Rocky Mountain spotted fever, tsutsugamushi and trench fever— which are sometimes referred to etiologically as the Rickettsia diseases. In each instance the virus is spread by a blood-sucking arthropod. An exanthem is present in each disease. One attack confers immunity. The mortality, however, varies, being very high in tsutsugamushi and practically *nil* in trench fever.

[2] *Am. Jour. Trop. Med.*, 1923, **3**, 529.

five days. A leukopenia is present. The course of the disease is from two to three weeks. The mortality is from 10 to 62 per cent. One attack confers a moderate degree of immunity. The *treatment* is symptomatic. The serum of monkeys which have recovered from the disease seems to have some value (Hayashi and Nagayo). Prophylaxis consists in wearing protective clothing, disinfection of clothing used in infected fields, and burning down the bushes and grasses in the endemic areas before cultivation.

ONYALAI

This disease occurs among the natives in Portuguese West Africa. The cause is unknown. The clinical features are characterized by sudden onset with fever, vesicular eruption on the mucous membrane of the mouth, and hematuria. The vesicles and small blebs in the mouth frequently contain blood. The tongue is swollen and painful. The skin may show hemorrhages. In the milder cases recovery usually occurs in one to two weeks. There is a tendency to recurrence. *Treatment* is symptomatic. Arsenic in full doses has been advised (Wellman).

BIG HEEL

This disease, also known as endemic hypertrophy of the os calcis, is found among the young adult natives of the Gold Coast of West Africa and Formosa. It is characterized by a somewhat sudden onset of fever followed by pain and tenderness in the heel with unilateral or bilateral swelling of the os calcis. Permanent thickening of the bone may follow an acute attack. The *treatment* is symptomatic. For the excessive enlargement of the os calcis in chronic cases surgery may be necessary.

GOUNDOU

This condition, also known as big nose or dog nose, occurs chiefly among the natives of Western Africa. It has also been found in China, the Malay Peninsula, and South America. Its specific cause is not known. It is characterized by the formation, usually early in life, of symmetrical bony tumors originating from the nasal processes of the superior maxillary bone. These give rise to the characteristic prominence of the nose, headaches, and not uncommonly a nasal discharge containing pus and blood. Nasal obstruction and interference with vision may occur. The overlying skin is normal. The tumors tend to progressive enlargement. The treatment is surgical.

AINHUM

Ainhum is a chronic local disease characterized by the formation of a furrow at the digito-plantar fold of the fifth toe which deepens and extends until the toe is encircled and finally severed from the foot. The other toes are rarely involved. Ainhum is found in South America, the West Indies, the West Coast of Africa, and rarely in other parts of the world. Occurring chiefly among adult male natives, it has been ascribed to injury or irritation of the bare feet. Castellani and Chalmers are inclined to believe that the condition is parasitic, although the specific agent has not been

isolated. A hereditary tendency has been noted (Weinstein). *Pathologically* it is characterized by a fibrous tissue constriction, an absorption of bone, endarteritis, and an increase in the adipose tissue of the toe. *Clinically* the distal portion of the toe is enlarged and bulbous in appearance, painless, and in the later stages hangs limp from the foot with which it is connected by a fibrous cord. Walking is difficult, ulceration may occur, and after several years the toe drops off. There are no general symptoms. It is easily distinguished from leprosy by the absence of signs of leprosy in other parts of the body. Prevention consists in cleanliness and the wearing of protective footwear. In the *treatment* of early cases vertical incisions through the constricting band have been proposed. Later amputation is necessary.

GANGOSA[1]

This disease occurs among the natives of the West Indies, Fiji, British Guiana, Guam, etc. Gangosa is a Spanish work meaning muffled voice. At various times the disease has been considered as related to syphilis and yaws. Others believe it to be a separate disease of unknown etiology. It is characterized by an ulceration of the palate which gradually extends and destroys the hard and soft tissues of the nose, palate, pharynx, and mouth. There is pain and an offensive discharge is present. In those instances in which the active process subsides cicatrization occurs. The Wassermann reaction is not infrequently positive, otherwise the blood examination shows nothing of note. In *treatment* the use of arsphenamine and mercury has been followed by strikingly beneficial results. Potassium permanganate solutions are useful for the offensive discharge.

TRENCH FEVER

This disease is now of historical interest only. During the World War approximately 800,000 cases occurred in four years among the allied troops in France. It is a relapsing fever probably caused by *Rickettsia quintana*. The infectious virus is conveyed by the excreta or crushed bodies of infected lice (*Pediculus corporis*), the virus entering through the broken skin (louse bites and scratches). Since recovery is almost invariable, pathological studies have not been made. Clinically the disease is characterized by a sudden onset with chilliness, fever, generalized pains and particularly *tenderness of the shins*. The temperature rises quickly to 101° to 104° F. and lasts from twenty-four to forty-eight hours and is followed by remissions of about five days with relapses of decreasing severity and finally recovery. Six or seven relapses may occur. Herpes, a faint macular rash over the chest and abdomen, enlargement of the spleen, and leukocytosis occur. The diagnosis has to be made from influenza, dengue, relapsing fever, typhus, malaria, rat-bite fever, etc. The mortality is *nil*. Convalescence may be protracted with symptoms of neurasthenia and disordered action of the heart. Prevention consists in attacking the louse problem and the treatment is symptomatic.

[1] W. M. Kerr has recently stated that the term gangosa should be eliminated from the nomenclature of tropical medicine, and that the ulceration which the term is employed to describe, should be placed in the category of late syphilis or late yaws (*Trans. Am. Soc. Trop. Med.*, 1922, 2, No. 4, 353).

PART II

PROTOZOAN INFECTIONS

CHAPTER X

AMŒBIC DYSENTERY

By RICHARD P. STRONG, M.D.

Synonyms.—Amœbic Colitis; Amœbic Enteritis; Entamœbiasis.

During the past twelve years (since the second edition of this work), an unusually large amount of investigation has been done on amœbic dysentery. Very extensive researches have been carried out on the amœbæ of the human intestine, their classification, differentiation and the method of the disease and its treatment. Perhaps the greatest progress of value to the clinician has been made in treatment, and amœbic dysentery is now one of the few diseases for which a specific method of treatment is available.

Definition.—An infectious disease characterized by a variable mode of onset, a course of great irregularity, intestinal disturbances consisting chiefly of intermittent attacks of diarrhœa, abdominal pain and the presence of amœbæ, and frequently of mucus and blood in the dejecta. Besides man, in the tropics monkeys and orangoutangs are sometimes attacked, and certain rodents may serve as carriers of the parasite.

During the past few years valuable contributions upon the zoölogical problems in relation to human amœbæ have been made by Wenyon and O'Connor[1] (1916–1917), Dobell[2] (1919–1921), Kofoid (1923–1924), Boeck and Stiles (1923) and others. The investigations of Lynch, Brug, Kessel, Kofoid and Chiang have demonstrated that rats may serve as carriers of the parasites of amœbic dysentery.

Etiology, Distribution and General Prevalence.—Amœbic dysentery has a wide geographical distribution. It has been found to be very prevalent in nearly all tropical and subtropical countries where it has been sought for and also occurs not infrequently in many countries with temperate climates. In America it is an important disease in the southern United States. Simon[3] states that the disease has shown a steady increase during the past fifteen years in the United States, and that it is especially prevalent in the South and in that portion bordering

[1] *Human Intestinal Protozoa in the Near East*, London, 1917.
[2] *The Amœbæ Living in Man*, London, 1919.
[3] *Tice's Practice of Medicine*, 1920, **4**, 271.

on the Gulf of Mexico. Craig reported an acute outbreak among the American soldiers stationed on the border of Mexico in 1916. Dock found the disease very prevalent in Texas, Florida and Georgia, and that in Texas it was more common than any other variety of illness. Reed found an unusually high incidence of infection in California, the sources of which are chiefly immigrants or tourists from the Orient and from Mexico. Sporadic cases occur from time to time in the New England States as well as in the central and western states; in fact, occasional cases have been reported from practically every section of the country. Blake and Hiscock in 1923 reported 9 cases of the disease in Connecticut, 2 complicated with liver abscess, and Dowling in 1923 reported 30 cases from Seattle, Washington. The disease has been reported specifically from twenty-six states and the District of Columbia. In view of these facts, and particularly on account of the constantly increasing travel to and from exotic countries, practitioners may expect to not infrequently encounter cases of this disease in almost any part of the United States.

Some fear was expressed that a great increase in amœbic dysentery had occurred and that a further increase would occur in the United States as a result of the World War. The statistics of Kofoid obtained through examination of both overseas and home, service men, showed an incidence of *Entamœba histolytica* of 20 per cent. in the men who had served overseas, and 4 per cent. in the home, service men, and it was estimated that several hundred thousand had become infested with *entamœba*. In still later examinations of ex-soldiers in California he found an incidence of infection with cysts of *Entamœba histolytica* in 67 per cent., and that this infection was more than twice as common as in home, service men. He concluded that the number of carriers of this parasite in the United States had been greatly increased by the infections in soldiers from overseas.

Stiles was not able to confirm the fact that there had been a marked increase of the disease in the United States since the ending of the World War. He addressed a letter of inquiry, asking whether any increase in amœbic dysentery had been observed, to 607 hospitals and 115 medical schools. Replies were received from 468 hospitals and 71 medical schools, representing every state in the Union except 4. Only negative replies were received from 28 states, and negative and indefinite replies were received from 3 other states. Thus, in at least 31 states there was no clinical evidence indicating that amœbic dysentery had increased to an extent that it had attracted attention in hospitals and medical schools. Among 532 replies for 44 states, 24 answers, or 4.5 per cent., reported an increase, but not in a manner to give rise to serious concern. Stiles then made a comparative study of immigrants, American boys and girls, civilians and soldiers who did not serve abroad, and of soldiers who had returned from Europe, and concluded that on an average the soldiers who served in Europe were not infected with the amœbæ of dysentery any more than certain other elements of our population. An examination of 13,043 specimens from 8029 persons in 48 institutions, located in 22 states and the District of Columbia, disclosed that 4.1 per cent. were infected with the cysts of *Entamœba histolytica*, and 39.9 per cent. showed

infection with protozoa. Every state which sent in a fair number of specimens showed the presence of the protozoön of amœbic dysentery. Stiles concludes that the rates of infection are higher than was recognized before the World War. He points out that these intensive studies on intestinal protozoa bring out two facts very clearly: (1) At least in temperate climates, the intestinal protozoa of man are by no means of so much clinical importance as has been even assumed; (2) at least in temperate climates, *Entamœba histolytica* is not usually a serious parasite and its presence in healthy carriers is common.

On the American continent the disease has been found to occur particularly in Mexico, Central America, the Canal Zone, Colombia, Venezuela, Ecuador, Peru, Chili, parts of Argentine and Brazil. At Sao Paulo 35 per cent. of the cases of intestinal disturbances were amœbic dysentery.

In Europe the disease is common, particularly in Spain, Sardinia, Malta, Italy, Greece and Turkey. It has also recently been very prevalent in parts of Russia and Galicia; during 1923–1924 it has been exceedingly prevalent in Poland and eastern Galicia, Cracow and Lodz. Popper reported that in Galicia most of the cases of dysentery were of the amœbic type. Yakimoff found many cases of this form of the disease in Russia as well as Turkey. Studies made particularly during the World War demonstrated that the disease occurs only occasionally in persons who have never been out of England or France.

In Asia the disease is especially prevalent in India, Palestine, Syria, Mesopotamia, southern China, Siam, Malay States and the East Indies, Cochin China, the Philippines, Shanghai, Formosa and in the southern portions of Japan and Korea. In Australia, cases of the disease have occurred particularly in New South Wales and Queensland.

In Africa the disease particularly prevails in Egypt, British East Africa, the Belgian Congo, Togo and Senegal and the North African States of Morocco, Tunis and Tripoli; in fact, the disease has been found to occur in those portions of Africa in which it has been especially sought for.

Amœbic dysentery is one of the most prevalent and important diseases of tropical and subtropical countries. While generally speaking it is the commonest form of dysentery in tropical countries, this is not always found to be the case during certain periods. For at certain seasons of the year, and during some years, bacillary dysentery may become epidemic and greatly change the ratio between these two forms of the affection. In the Philippine Islands, during 1899–1900, an epidemic of bacillary dysentery occurred, and in a series of 147 cases of bacillary and amœbic dysentery 67 per cent. belonged to the latter variety. Of the dysentery cases encountered by the writer in Manila during fourteen years, fully 60 per cent. were amœbic, and the great majority of the fatal cases of dysentery in adults showed lesions of this form at necropsy. The disease at that time was the most prevalent one in the Philippine Islands among white people. However, during later years the percentage of amœbic dysentery among white patients steadily decreased in the Philippine Islands, largely owing to greater hygienic precautions exer-

cised. Deeks and James[1] pointed out that in the Panama Canal Zone there had been a marked decrease in the number of amœbic dysentery cases for similar reasons. Rogers[2] showed that in India the amœbic form of dysentery is by far the most prevalent type and that more deaths occur from this form. In Siam and the Malay States, Fraser found 30 per cent. of 1819 cases of dysentery to be amœbic, but more recently Fletcher and Jepps in 983 cases of dysentery in the Federated Malay States found only 20 per cent. to be of the amœbic variety. In the Canal Zone, Deeks reported 19 per cent., and in Brazil, Ficker found 35 per cent. of the dysenteries to be of the amœbic variety.

Meteorological Conditions.—These have considerable influence upon the prevalence of the disease. In the Philippine Islands by far the greatest number of cases is recognized between June and September, the largest number appearing after the heavy rains have begun. Harris states that the onset of the malady in the United States is almost invariably in the summer months, while Simon in the United States found that the incidence of the disease is greatest during April and May, with a steady decline during the summer months, and a further rise in the early fall extending well into November. Rogers concluded that the prevalence of dysentery in India closely corresponds with the rainy season, the curve declining steadily with a cessation of the rains late in October. Heavy and especially prolonged rainfall favors the transmission of the infection both by preserving the cysts of the amœbæ, which are killed by thorough drying, and by causing them to be washed from the soil and cesspools into water supplies.

While the influence of temperature upon the spread of the disease is not so important as moisture, amœbic dysentery is much more common generally in warm countries than in cold ones, and the cysts of amœbæ are usually better preserved in a warm as well as a moist climate. Carnegie Brown and Simon believe that the tendency of amœbic dysentery cases to relapse is augmented by cold weather, and Simon found that the relapses in his patients were especially prone to occur during the cool spring or autumn weather. While the disease is more commonly one of low-lying countries and poorly drained districts, it is by no means uncommon in some of the hill stations in the tropics with altitudes up to 5000 feet.

Sex.—It is generally agreed that the disease is much more prevalent in males. In Futcher's series of 119 cases at the Johns Hopkins Hospital there were 108 males and 11 females. In the Philippine Islands the disease occurs more frequently in males. In the Manila Government Civil Hospital in 401 cases the ratio of males to females was 4.1 to 1. In 200 personal cases only 23 were in females. Simon in a series of 217 cases found 180 males and 37 females, while Carnegie Brown in the returns from government hospitals in the eastern tropics, found 5 males to 1 female. This prevalence in males seems to be due to the fact that males in the tropics are more exposed to infection, rather than to any sex predisposition.

[1] *Am. Jour. Trop. Med.*, 1925, 5, 97.

[2] *Lancet*, 1912, ii, 1062.

Race.—All races in the tropics are liable to attack, though the white race appears to be much more susceptible than the Malay. However, predisposition of the native races depends considerably upon their habits of life. The better class of Chinese residents who drink only hot water or tea are very rarely infected. Malays, who by their mode of life are frequently exposed to infection, do not suffer so often, or usually as severely as Americans and Europeans. Futcher and Harris found that in the United States blacks were less frequently attacked than whites. Simon found in a series of 217 cases that 165 were whites and 52 were negroes, but that this ratio corresponded with the population figures of whites to blacks for the district from which most of the cases come. He does not believe that racial susceptibility plays a very prominent role.

Age.—While amœbic dysentery occurs at all periods of life, the greatest number of cases occur in the third and fourth decade, which corresponds to the period of greatest economic activity. In Simon's series of 217 cases the average age was thirty-four years. Of the writer's 200 cases studied in the Philippine Islands the disease developed in 149 when they were between twenty and forty years of age. In Futcher's series the greatest number occurred between the ages of twenty-one and thirty years. In the Malay States the average age of half of the patients treated was from twenty to thirty years. After forty years the case incidence everywhere falls rapidly. In the tropics it is usually between the ages of twenty to forty years that men are exposed more to the risk of infection, and these variations in incidence are evidently due particularly to the opportunity for and exposure to infection rather than to the period of life. In the tropics the disease is not uncommon in children under ten years of age. Futcher calls attention to 11 cases; Musgrave encountered 21 with 1 death in a series of 100; the writer met with 18, while Harris reports 4 cases out of 35 in young children.

Unhygienic Influences.—It has been stated that amœbic dysentery is an affection especially of the poor, and is almost always associated with filth, bad hygienic surroundings and lack of proper food. This does not hold good in the tropics, as, for example, in the Philippine Islands, or in India or Egypt; all are likely to be attacked who do not take proper precautions in regard to drinking water and food. Vegetables and fruits which have been in contact with the soil, which may be a repository for amœbic cysts, constitute special elements of danger, particularly in countries where the soil is fertilized with human excrement. Susceptibility seems to depend considerably in some cases upon the general physical condition, although sometimes apparently perfectly healthy and robust persons are attacked.

The Amœba of the Human Intestine.—These organisms are classified under the rhizopoda of the protozoa. They are unicellular parasites possessing an endosarc and ectosarc which usually can readily be distinguished when the organism is in motion. The endosarc is granular, and usually encloses several vacuoles of variable size. The ectosarc is clear and more hyaline in appearance. When seen in the feces the pathogenic form frequently contains red blood corpuscles. Pigment

granules and bacteria have also been observed in the endosarc. The parasite moves by means of pseudopodia; blunt processes consisting of the ectosarc are first protruded and into these protrusions the protoplasm of the endosarc appears to flow. The nucleus may sometimes be observed in the living forms but can be more clearly seen in stained preparations. For bringing out the structure of the parasite in smear preparations made from the stools or from cultures, iron hematoxylin, Delafield's hematoxylin and borax carmine are all satisfactory. The preparations should be fixed while moist. For staining the amœbæ in sections after proper fixation, Giemsa's stain, as modified by Wolbach,[1] is recommended.

Biological Properties.—It is only recently that satisfactory proof of the cultivation of the pathogenic amœbæ has been given, and even in these cultures the amœbæ have not been grown free from bacteria. In 1885 Kartulis reported successful results in the cultivation of amœbæ in pure culture free from bacteria. He used a straw decoction as a medium and stated that he obtained a pure growth in cultures made from an abscess of the liver which contained amœbæ but which was free from bacteria. This work has never been confirmed. Williams reported the cultivation free from bacteria of amœbæ found in the intestine of mammals upon crushed brain, liver, kidney and other tissues of the rabbit or guinea-pig streaked on nutrient agar. Couret and James Walker claimed that they cultivated five varieties of intestinal amœbæ from cases of dysentery after having separated them from associated bacteria by the use of a special medium to which sterile autolyzed tissue fluid had been made. This was obtained by exposing sterile brain, liver or other tissues in the sterile thermostat for from ten to twenty days at a temperature of 40° C. The media should not be too acid, not over 1.5 per cent., and the surface of the agar should be broken up before use. They explain previous failures at cultivation by the absence of autolyzed tissues which they believe the entamœbæ require for their growth. In the body they consider that certain bacteria aid the growth of the amœbæ by autolyzing tissues.

Other investigators have not been successful in cultivating amœbæ free from bacteria, and many believe that bacteria are necessary for the growth and multiplication of the amœbæ, while others believe that a symbiotic relationship exists between the amœbæ and associated bacteria. Such a symbiosis, however, has not been satisfactorily demonstrated. The free-living amœbæ may be easily grown upon a great variety of media together with bacteria, providing the substance used does not offer conditions so favorable for the growth of bacteria that they overgrow and prevent the development of the protozoa. Dilute peptone solution constitutes a very favorable fluid medium.

From recent experimental work it was concluded that all the species of amœbæ cultivated on various media were free-living species and that the true parasitic species of the human intestine had not been cultivated. Dobell particularly insisted that the dysentery amœba, *Entamœba*

[1] *Jour. Med. Res.*, 1912, **27**, 83.

histolytica, cannot live and multiply outside of the human intestine. Cutler[1] reported the cultivation of *Entamœba histolytica* from 3 human cases of amœbic dysentery, and of one strain of amœbæ from a cat infected with the cysts of *Entamœba histolytica* from one of his cultures made from a human case of dysentery. The media he employed was made with the white and yolk of an egg to which a few drops of blood were added. He obtained 6 positive cultures in 45 trials, and the morphology of the amœbæ cultivated, as demonstrated by his figures, corresponded to the morphology of *Entamœba histolytica*. All of Cutler's cultures were carried through daily or forty-eight-hour transfers over a period of several weeks. One strain was living at the end of eight months, but all other strains died after a few weeks on artificial media. In a second paper he gives his observations on the cultivation of *Entamœba histolytica*, using material from his cultures and from cats infected with his cultures. Dobell was unable to confirm this work. Barret and Smith[2] successfully cultivated *Endamœba barreti* from the snapping turtle and *Endamœba ranarum* from the frog, and stated that they believed their method was applicable to other species of entozoic amœba.

In 1924 and 1925 Boeck[3] and afterward Drbohlav[4] and Chiang reported the cultivation of *Entamœba histolytica*, and the amœba cultivated was shown to be capable of producing amœbic dysentery in kittens. One strain retained its pathogenic virulence for cats during eight months and after more than 150 generations. The media employed by Chiang consists of: Four eggs, thoroughly washed in alcohol and broken aseptically into a sterile glass vessel containing glass beads; 100 c.c. beef broth is added to the mixture, and shaken thoroughly, to break the egg into fine particles; 3 c.c. of the mixture is poured into each tube and slants made in the inspissator. The inspissator is heated slowly to 100° C., then gradually cooled. The slants are next removed and placed in the autoclave for twenty minutes, at 15-pounds' pressure. After the slants have cooled for a few hours they are covered with 3 c.c. each of sterile Lock-Ringer solution. The media had a reaction of pH 7.6 to 6.8.

Behavior to Physical Conditions and Chemical Substances.—The resistance of amœbæ to physical conditions and chemical substances is of importance in connection with prophylaxis and treatment. The amœbæ of the intestine are usually destroyed by a temperature of 60° C. maintained for one hour even when encystment has occurred. Boeck determined that the approximate thermal death-point after exposure of five minutes of the cysts of the human amœbæ is as follows: *Entamœba coli*, 76° C.; *Entamœba histolytica*, 68° C.; *Endolimax williamsi* (*Iodamœba butchlii*), 64° C.; *Endolimax nana*, 64° C. The vegetative forms of amœbæ usually lose their motility in the stools and undergo disintegration in a short time after the stool is passed. This is particularly the case if the stools are kept at low temperature. However, when

[1] *Parasitology*, 1919, **11**, 127; *Jour. Path. and Bacteriol.*, 1918, **22**, 22.
[2] *Am. Jour. Hyg.*, 1924, **4**, 155.
[3] *Bull. Soc. Path. Exot.*, 1925, **18**, 121.
[4] *Proc. Nat. Acad. Sci.*, 1925, **11**, 235.

encystment of the amœbæ occurs, freezing for as long as a month may not destroy them. The cysts do not appear to withstand thorough drying for any length of time, for after becoming dry they stain at once with dilute eosin and when cysts stain in this manner they are probably dead. Bercovitz[1] found (1924) that staining with hematoxylin is of more value than with eosin in the determination of the viability of the cysts of human intestinal amœbæ. When putrefaction in the dejecta is rapid the cysts may remain alive for a few days only. They sometimes remain alive longer in formed stools than in soft or liquid ones, since in the latter fermentation often proceeds more actively. *Endamœba histolytica* cysts have been found apparently viable at the end of a week in the stools. In some instances the cysts have survived for over a month in water which has been mixed with feces, particularly if the dilution with water is sufficient to prevent intensive bacterial growth. Stiles found that the lower the temperature, the longer the cysts survive, and that this was due to the fact that the low temperatures inhibited bacterial growth and consequent putrefaction. Boeck[2] found that under artificial conditions, such as immersion of the cysts in distilled water in bottles left at a temperature of 12° to 22° C., the cysts of *Entamœba histolytica* were found viable at the end of one hundred and fifty-three days, and of *Entamœba coli* at the end of two hundred and forty-four days. The determination of the viability was based upon the property of the cyst to resist staining with eosin solution as well as the morphological appearances.

The action of various *chemical* substances upon amœbæ is of particular importance with reference to treatment as well as in connection with disinfection of the stools. Harris found that amœbæ in the stools were killed within ten minutes by a 1 to 300 solution of quinine bisulphate, but that the amœbæ were often unaffected by saturated solutions of quinine sulphate. Rogers found in scrapings from the walls of amœbic liver abscess that a solution of quinine of 1 to 1000 failed to kill the parasite even after several hours, but a 1 to 500 solution stopped all movement of the amœbæ in from five to fifteen minutes. In order to test if such a strength would be effective when applied to the living wall of an abscess, a piece of such tissue full of active amœbæ was placed in a solution of 1 to 500 sulphate of quinine in normal salt solution, and scrapings examined every five minutes. In none were any living parasites found.

Musgrave and Clegg found that when a slant culture of amœbæ with bacteria was treated with a 1 to 2500 solution of quinine hydrochloride, the parasites quickly encysted and in from five to eight minutes many had broken up and disappeared. Ten minutes later cultures were made but no development of amœbæ occurred, although the bacteria grew out well. In an experiment with another amœba a slight growth was observed. Acetozone, 1 per cent. acid to phenolphthalein, in solutions of 1 to 5000 and 1 to 2000, always killed the amœbæ in cultures.

According to Vedder, the fluidextract of ipecacuanha destroys amœbæ

[1] *Univ. California Pub. Zoöl.*, 1924, **26**, 249.
[2] *Am. Jour. Hyg.*, 1921, **1**, 527.

in a solution of 1 to 10,000 or in some instances 1 to 100,000, while he found that de-emetinized ipecacuanha was practically inert against amœbæ. Wherry found that emetine in 1 to 20,000 dilution killed the motile forms in cultures of amœbæ in only 1 of 5 experiments after twenty-three hours' exposure at 36° to 38° C. None of the amœbæ was killed after one hour exposure. Lyons found that on cultures of amœbæ ipecac apparently possessed but slight inhibitive power on the amœbæ.

Bowman and the author studied in a comparative way the effects of suspensions of ipecac and of solutions of emetine and quinine sulphate upon different cultures containing either motile or encysted forms of a free-living species of amœba isolated from human stools and upon motile amœbæ in the stools of dysenteric cases. A suspension of ipecac, 1 to 25 in distilled water, destroyed all the motile amœbæ in cultures within twenty-four hours and subsequently amœbæ did not develop from the cysts treated in this way. In the parallel cultures treated with quinine sulphate solution of 1 to 1000 all the motile amœbæ were destroyed, but in 1 of the 3 experiments amœbæ developed from the cysts which had been in contact with the solution. In the control cultures motile amœbæ were abundant. In a second series of experiments with an ipecac suspension of 1 to 1000 and quinine sulphate solution, 1 to 1000, the ipecac suspension failed to kill the motile amœbæ in all of the tests, while the quinine sulphate solution did so. In all the experiments of this series, however, amœbæ developed from the cysts which had been in contact with these substances. In a third series in which the cultures were treated with ipecac suspension, 1 to 500, and quinine sulphate solution, 1 to 1000, the ipecac suspension destroyed all the motile amœbæ in 1 of the tests but failed to do so in 2 instances. Amœbæ developed from the cysts so treated in all 3 of the experiments. The quinine solution destroyed the amœbæ in all 3 of the experiments, but amœbæ developed from the cysts which had been in contact with the quinine solution in 1. In a fourth series, with a solution of emetine, 1 to 50, all the motile amœbæ were destroyed and no amœbæ developed later from the cysts which had been in contact with the emetine solution. Allan found that solutions of emetine in dilutions weaker than 1 to 2000 in the space of one to two hours, when applied to entamœbæ in cover-glass preparations, did not affect the appearance or motility of these organisms, and often dilutions as strong as 1 to 150 failed to kill them in this time.

Sellards and Leiva[1] found that emetine hydrochloride in the dilution of 1 to 1,000,000 gave complete inhibition of growth of cultures of amœbæ of the *Limax* type; that quinine dihydrochloride in a dilution of 1 to 100,000, benzyl benzoate in a suspension of 1 to 50,000 and *Castela nicholsoni* in a dilution of 1 to 5000 also gave complete inhibition of growth of the amœbæ, though with *Castela nicholsoni* in this dilution the results were reported as somewhat variable.

All of these experiments showed that either ipecac or emetine destroyed amœbæ *in vitro*. The different results obtained by the different authors

[1] *Jour. Pharmacol. and Exper. Therap.*, 1924, **22**, 467.

with these substances in different dilutions may have depended partly upon the reaction of the solution, and partly upon the age and number of cysts of the amœbæ in the cultures employed.

Dale and Dobell found that injections of emetine had absolutely no effect on clinical amœbic dysentery in the cat, and that this drug was not particularly toxic when applied directly to the entamœbæ. However, the investigations of Vedder, Wherry, Bowman and the writer, and Sellards and Leive demonstrated that both emetine and ipecacuanha have a decided effect in directly destroying amœbæ and their cysts.

Dale has found that dimethoxy emetine is ten times as poisonous for the amœbæ *in vitro*, and not nearly as poisonous for animals as emetine, but that it has no therapeutic effect whatever. He concluded that the curative action of these alkaloids was not proportional to their direct poisonous action on the patient, and suggested that the body of the patient must play an essential and perhaps a primary part in the killing of the parasite. The experimental difficulties in connection with the chemotherapeutic study of emetine in cats infected with amœbæ are considerable, and it is desirable that the problem should be approached in other ways. Sellards and Leive found that experimental amœbic dysentery in cats responds to emetine in fundamentally the same way as the spontaneous disease in man.

The action of chemical substances upon the cysts of amœbæ is of much importance both in connection with the treatment of carriers of *Entamœba histolytica* as well as disinfection of the stools. The cysts of *Entamœba histolytica* often offer considerable resistance to certain disinfectants. Stiles found that these cysts appeared to be viable as long as five days in 5 per cent. formalin, and that in a 1 per cent. solution of sodium chloride some of the cysts of *Entamœba coli* were alive at the end of two days. The cysts were held to be dead when disintegration occurred. Bercovitz found, judging from the morphological appearances of the cysts and their staining reactions, that the cysts of *Endamœba coli* and *Councilmania lafleuri* were killed by treatment with bichloride of mercury, phenol, lysol, or formalin, all in a strength of 1 per cent. after exposure for one hour.

Wenyon and O'Connor found that cresol killed all cysts immediately in a strength of 1 to 20, in one minute in a strength of 1 to 30, in one-half hour in a strength of 1 to 100 and not at all in dilutions of 1 to 2000. Cresol therefore can apparently be employed for the disinfection of dysenteric stools or for the hands of those who have to care for patients. Acid sodium sulphate tablets and chlorinated lime tablets used for the purification of water, according to their experiments, failed to kill the cysts of amœbæ, hence the boiling of drinking water or the use of distilled water in districts where the disease prevails widely is recommended.

Kessel[1] has found that the maximum percentage of free chlorine in water in which growth of coprozoic forms of amœba was obtained was 2 per cent. In stronger solutions on an exposure of ten minutes no growth occurred.

[1] *Jour. Parasitol.*, 1925, **11**, 153.

The Distribution of Amœbæ in the Body.—The amœbæ in man are most commonly found in the large intestine, but they have been repeatedly observed in the abdominal cavity and neighboring tissues and in abscesses of the liver, lung, pleura and brain. Their occurrence has also been reported in a form of arthritis deformans, in the glands in Hodgkin's disease, in bronchitis, in the testes and epididymes, in the pelves of the kidneys and ureters, in ovarian abscesses and salpingitis, in subcutaneous tissues, in perineal sinuses, in the bladder and urine, in necrosis of the ribs or jaw bone, in abscesses of the mouth, in pyorrhœa alveolaris, and in tartar scraped from the teeth. Whether the amœbæ reported by Flexner and others in malar abscesses were of the species *Entamœba gingivalis* or *Entamœba hystolytica* is not clear. Often when the amœbæ are present in the bladder or urine there has been a sinus connecting with the intestine, but this has not always been the case. Early reports of instances of infection of the bladder and urine with amœbæ were made by many observers. Cases of infection of the bladder and urine have been reported recently by Reiss,[1] Worsley,[2] Petzetakis.[3]

A number of publications have appeared not only upon the subject of *pulmonary amœbiasis* with the presence of amœbæ in the sputum, in which case abscess of the lung was present, but upon *bronchial amœbiasis*. This last is a condition in which an invasion of the bronchi by the amœbæ is said to have occurred. Such cases have been reported in 1924 and 1925, particularly by Panayotatou[4] and Petzetakis,[5] but whether amœbic bronchitis exists as a primary infection seems to be somewhat doubtful.

A number of cases of *cutaneous* infection with amœbæ have been reported. Dagorn and Heyman reported a case in which the wound following operation for liver abscess became phagedenic and in the pus of small cutaneous abscesses about it many living amœbæ were found. Other observers, as Runyan and Herrick[6] have also reported similar cases of infection of the skin and spreading ulcerations following operations for liver abscess. In Heimburger's[7] case the liver abscess ruptured externally through the abdominal wall and the amœbæ were found in the walls and pus of the ulcer which developed in the skin. Sharp and Morrison[8] (1925) reported in Nigeria the presence of amœbæ in multiple deep abscesses of the muscles.

Mills[9] and Vilacoro have inferred that amœbic iritis and iridocyclitis may be brought about through the absorption of toxins from intestinal amœbæ. However, the evidence for this inference is far from convincing. Further confirmation of the work of Kofoid and Swezy who reported the presence of *Endamœba dysenteriæ* in the bone lesions in arthritis deformans and in the lymphatic glands in Hodgkin's disease is desirable. Recently they investigated the possibility as to whether *Endamœba gingivalis* was the amœba in the bone-marrow in arthritis deformans and

[1] *Arch. f. Schiffs u. Tropen-Hyg.*, 1924, **28**, 334.
[2] Worsley and Bateman: *Jour. Trop. Med. and Hyg.*, 1924, **27**, 278.
[3] *Bull. et mém. Soc. méd. de hôp. de Paris*, 1924, **48**, 1227.
[4] *Bull. de l'Acad. de méd.*, 1923, **90**, 305.
[5] *Bull et mém Soc. méd de hôp. de Paris*, 1923, **47**, 1431.
[6] *Am. Jour. Trop. Med.*, 1925, **5**, 137.
[7] *Arch. Dermat. and Syphil.*, 1925, **11**, 49.
[8] *Brit. Med. Jour.*, 1925, p. 205.
[9] *Arch. Ophthal.*, 1923, **52**, 525.

in Hodgkin's disease, and concluded that *Endamœba dysenteriæ* was the amœba present.

Smith (1924) in a study of 180 cases of amœbic dysentery reports 1 with pain and swelling in the left knee in which active amœbæ were found in the pus. In Warthin's case in which amœbæ were found in the epididymis and testes, with definite though slight local lesions in these organs, the patient had been affected for many years with amœbic dysentery. The amœbæ in the testes, Warthin reports, corresponded in every way to those previously found in the stools, and were identified as *Entamœba histolytica*. Hines reported a case of amœbic dysentery in which *Endamœba histolytica* was found during life in the seminal fluid.

Classification and Description.—A large number of species of amœbæ have been found living chiefly in the digestive tract of man and many different animals, frequently as harmless commensals, but sometimes causing definite disturbances and disease. It therefore is necessary to have some knowledge of the classification and means of differentiation of of these amœbæ. Unfortunately, the amœbæ found in man have been classified in many different species, and to these a multiplicity of names has been given. Stiles and Boeck[1] have cited some forty-four names, but unanimity of opinion in regard to nomenclature has not been reached. One of the present problems is to combine a method by which it is possible to give physicians a more restricted classification which they can use for clinical purposes, with a broader classification which specialists can use for more permanent and constructive taxonomic use. As only a few writers have worked on a genotype basis, the generic nomenclature is somewhat confused. Today, greater importance than ever before is being placed by some authors upon nuclear characteristics in relation to generic value, and as this involves special technique, which is not always known to all workers, and as conceptions as to the generic value of these nuclear characteristics are not always clearly crystallized, the confusion is enhanced. Groups which some would consider as subgeneric, others evaluate as generic. There are few branches in zoölogy which are in such a confused state as respects nomenclature as are the amœbæ.

It is of advantage to review the important species which have been described. In 1879 Leidy established the genus of *Endamœba* for the parasitic species found in the common cockroach and named it *Endamœba blattæ*. In 1897 Cassagrandi and Barbagallo established the genus of *Entamœba* and named the species they encountered *Entamœba hominis*. Quincke and Roos, Kruse and Pasquale, Celli and Fiocca, and the writer, all recognized from morphological differences, from clinical observations, and especially from experiments upon animals, that more than one species of entozoic amœba occurred in man, and these species were described under a variety of names. From a zoölogical standpoint the evidence of the plurality of species was not entirely complete.

Schaudinn, in 1903, supplied zoölogical descriptions of these two species of amœbæ, describing them under the terms *Entamœba coli* and

[1] *United States Hyg. Lab. Bull.*, No. 133, 1923.

Entamœba histolytica. The second species was regarded as the cause of amœbic dysentery and amœbic liver abscess, and the first as a harmless inhabitant of the intestine. The cysts of *Entamœba coli* were described as containing 8 nuclei. Reproduction in *Entamœba histolytica* was described as occurring by binary fission or asexually by peripheral budding, in which small aggregations of chromatin reached the periphery of the cytoplasm and enclosed in a resistant capsule broke off from the apparent amœba and constituted the infecting stage. Subsequent investigations have shown that the description of the life cycles and many of the morphological details given by Schaudinn were incorrect.

In 1907 Viereck described a species of amœbæ found in 2 cases of dysentery in India, and which he named *Entamœba tetragena.* This species was shortly afterward described by Hartmann in cases of dysentery from Africa, and was subsequently found to have a wide distribution. It appeared to be the usual species encountered in cases of human amœbic dysentery. The sporocysts developed only 4 nuclei instead of 8 as in *Entamœba coli.* Subsequent investigations led to the determination that *Entamœba tetragena* and *Entamœba histolytica* are identical. These investigations appeared again to limit the human intestinal amœba to two species: *Entamœba histolytica* with 4-nucleated cysts and *Entamœba coli* with 8-nucleated cysts.

In 1917 Wenyon and O'Connor described a new species of amœba with 4-nucleated cysts (*Endolimax nana*). They pointed out that *Endolimax nana* might be confused with *Amœba limax,* but that the latter can be easily cultivated, while *Entamœba nana* resisted cultivation. The work of Wenyon and O'Connor with reference to the occurrence of this amœba in the human intestine has been abundantly confirmed. Kofoid recently found it to be the most common intestinal amœba in the stools of some American troops. Out of 1200 men *Endolimax nana* was found in 28 per cent., *Entamœba coli* in 23 per cent. and *Entamœba histolytica* in 9.3 per cent. While the species is regarded as non-pathogenic, it is of importance on account of the possibility of its being confused with *Entamœba histolytica.*

In 1921 Kofoid and Swezy[1] described another species of human intestinal amœba which is parasitic and probably pathogenic, under the term *Councilmania lafleuri.* For this species they created a new genus which they state is distinguished by characteristics which no other parasitic amœba presents. The cysts contain 1, 2, 4 or 8 nuclei, from which cytoplasm emerges through a pore in the cyst wall as a chromphile bud. A nucleus migrated into the bud which detaches as an amœbula. This amœba was often seen to contain red blood corpuscles and is supposed by Kofoid to have a wide geographical distribution.

In 1924 Kofoid and Swezy[2] reported 3 instances of infection of man by still another new species of amœba, *Karyamœba falcata* (gen. nov. sp. nov.). The organism was found in the feces, and in all 3 cases it was accompanied by *Endamœba dysenteriæ* so that the authors state the relations to the host were complicated. This amœba persisted after treat-

[1] *Univ. California Pub. Zoöl.,* 1921, **20**, 169.
[2] *Ibid.,* 1924, **26**, 221.

ment for amœbiasis with no clinical signs of pathogenicity. It did not appear to be a coprophile contamination but rather a persistent inhabitant of the human bowel. It occurred in the motile phase only. Mitosis and binucleate amœbæ and rounded-up precystic phases were found. The authors state that there is no other amœba known to them which has the nuclear structure of this organism, specifically the crescentic siderophile structures in which the peripheral chromatin is grouped. There was no trace of a blepharoplast in the cytoplasm and no flagellate phase was found in the stools in the 3 cases studied. In the absence of the blepharoplast and a flagellate phase, it was judged to be one of the *Amœbidæ*, Doflein, 1916, and was placed in a genus coördinating with the genera *Endamœba* and *Vahlkampfia*. It differs from all other genera in this family in the position of the crescentic siderophile structures. While it is more closely related to *Vahlkampfia*, it differs in the small size and eccentric location of the karyosome and in the abundance and crescentic masses of the peripheral chromatin. They further state that it is not possible to include it in *Vahlkampfia* without making a heterogeneous assemblage of nuclear types therein.

Faust[1] created a new genus *Caudamœba*, and described a new species, *sinensis*, which was encountered in cases with symptoms of amœbic dysentery. Faust states that the organism is characterized by viscous endoplasm, thin layer of ectoplasm, antero-posterior polarity, lobose anterior and attenuate posterior end drawn out into a caudostyle, which is surrounded at times by a group of protoplasmic projections more or less conspicuous, a constant movement of the organism away from the caudal end, and a nucleus near the anterior end of the body with minute chromatin granules just within the nuclear membrane, together with a karyosome specifically different from that of the described entamœbæ of man. The organism was found in 4 dysentery patients from North China. It is phagocytic for red blood corpuscles and for bacteria and in 2 cases was the only microörganism in the stool suspected of being pathogenic. Patients having only this organism in the stools gave a typical history and had symptoms of amœbic dysentery.

In addition, a number of free-living non-parasitic species have been observed or cultivated on artificial media from human feces which may have been ingested and passed through the digestive tract in an encysted condition, or been deposited in the stools after they had been passed and have then emerged from their cysts. Thus Wells[2] found that in India, amœbæ of at least two types were commonly present in the air and that these could readily gain access to specimens of feces even though these were carefully collected. These free-living amœbæ for the most part are of the *limax* type and while they have been frequently confused with the human entamœba, they at least usually can be distinguished from these by certain differences in the life cycle, such as the type of autogamy, or by the presence of a contractile vacuole.[3]

In 1912 Chatton and Lalung-Bonnaire created the genus *Vahlkampfia*,

[1] *Jour. Parasitol.*, 1923, **9**, 221. [2] *Parasitology*, 1911, **4**, 204.

[3] Hartmann, Werner, Whitmore, *Arch. Protistenk.*, 1911, vol. **23**. Walker, *loc. cit.* Craig, *Am. Jour. Med. Sci.*, 1913, **145**, 83.

which included the great majority of easily cultivated amœbæ isolated by various observers from human stools and potable waters. Craig described still another species of amœba under the name of *Paramœba hominis*. For this species Calkins created a new genus known as *Craigia*, with *Craigia hominis* for the type species. This organism was said to possess both amœboid and flagellate stages in its life history, and probably to produce chronic diarrhœa or dysentery in man. It was later observed in Honduras by Barlow.

Guaducheau believes that *Endolimax phagocytoides* is a parasitic species of the intestine of man and constitutes a form of passage between the *Entamœba* which are culturable with difficulty and the free-living amœbæ which are easily cultivated, but Stiles classifies it as a synonym of *Endolimax nana*.

It is not advisable to enumerate here the numerous names which have been applied by various authors to the species of amœbæ which have been referred to in this article, or to include all of the doubtful species. Stiles and Boeck, 1923, in a *United States Public Health Report*, have compiled these, and the reader is referred to this publication for additional information. The following classification of genera and species includes the important amœbæ which have been recognized as infecting man, as well as several of less importance.

TABLE OF THE GENERA AND SPECIES OF THE AMŒBÆ OF MAN.

Genus I. *Entamœba* (Cassagrandi and Barbagallo, 1895.
(Löschia (Chatton and Lalung-Bonnaire)), 1912.
Type species: 1. *Entamœba coli* (Grassi).
2. *Entamœba histolytica* (Schaudinn).
(*Amœbæ dysenteriæ*) (Councilman and Lafleur).
3. *Entamœba gingivalis* (Gros).

Genus II. *Endolimax* (Kuenen and Swellengrebel), 1917.
Type species: *Endolimax nana* (Wenyon and O'Connor).

Genus III. *Pseudolimax* (Kuenen and Swellengrebel), 1917.
Iodamœba (Dobell), 1919.
Type species: *Pseudolimax bütschlii* (Prowazek).

Genus IV. *Craigia* (Calkins), 1912.
Type species: 1. *Craigia* (*Paramœba*) *hominis* (Craig).
2. *Craigia migrans* (Barlow), 1915.

Genus V. *Dientamœba* (Jeppe and Dobell), 1918.
Type species: *Dientamœba fragilis* (Jepps and Dobell).

Genus VI. *Councilmania* (Kofoid and Swezy), 1921.
Type species: *Councilmania lafleuri* (Kofoid and Swezy).

Genus VII. *Caudamœba* (Faust), 1923.
Type species: *Caudamœba sinensis* (Faust).

Genus VIII. *Karyamœba* (Kofoid and Swezy), 1924.
Type species: *Karyamœba falcata* (Kofoid and Swezy).

It should be stated that Castellani places *Entamœba histolytica, coli* and *gingivalis* in the genus *Löschia* of Chatton and Lalung-Bonnaire (1912), and *Endolimax nana* in the genus *Vahlkampfia* of the same authors, though the cyst of this species is binucleate. Attention must again be called to the fact that there is no unanimity of opinion regarding the entire classification of the amœbæ of man. Several observers refuse to recognize the genus *Craigia;* some authors believe that it belongs rather with the flagellates than with the amœbæ. Stiles and Boeck state that as yet no satisfactory generic diagnosis for *Endolimax* appears to be available since Dobell's new genus *Iodamœba* has not been adopted generally, as he has not yet clearly defined it except through its genotype. As they are not entirely persuaded as to its validity, they follow Kofoid and Swezy and Brug in accepting it as a synonym of *Endolimax* until it seems more formally established. Until we know more about *Dientamœba*, its position must be regarded as doubtful. So far no signs of division or of cyst formation have been observed in the type species described by the authors. Taliaferro and Becker reported a single case of infection with this species in a girl, aged three years, who was apparently healthy and without any intestinal disorder. The genus *Dientamœba* is said to be characterized by the presence of two nuclei. With reference to the genus and species *Councilmania lafleuri*, Wenyon[1] insists that this species is no other than *Amœba coli*, a view in which Gunn concurs. However, Kofoid and Swezy and Kessel[2] have carefully studied the question anew and insist upon its validity. Stiles and Boeck regard this genus *sub judice*. They further state that the genera *Endolimax, Councilmania* and *Dientamœba* might well have been proposed as subgenera rather than as genera. Wenyon also does not accept *Karyamœba falcata* or *Caudamœba sinensis* as valid species.

Dobell and O'Connor give the following key to the species of amœbæ parasitic in man. This key, however, does not include all of the genera and species referred to in this article.

KEY TO GENERA AND SPECIES.

1. (*a*) One nucleus present in active amœba, 2.
   (*b*) Two nuclei present, genus *Dientamœba*, 6.
2. (*a*) Nucleus with small spherical karyosome and peripheral layer of fine chromatin beads, genus *Entamœba*, 3.
   (*b*) Nucleus with large irregular eccentric karyosome, and no peripheral chromatin granules, genus *Endolimax*, 4.
   (*c*) Nucleus with large central spherical karyosome, surrounded by a layer of achromatic granules, genus *Iodamœba*, 5.
3. (*a*) Ripe cyst 4 nucleate; glycogen diffuse; large chromatoids generally present, *Entamœba histolytica.*
   (*b*) Ripe cyst 8 nucleate; glycogen dense, in early stages only; large chromatoids occasionally present, but often absent, *Entamœba coli.*

[1] *Trop. Dis. Bull.*, 1925, **22**, 333.
[2] *Univ. California Pub. Zoöl.*, 1924, **26**, 21.

4. Ripe cyst 4 nucleate; glycogen rarely present; chromatoids absent, *Endolimax nana*.
5. Ripe cyst 1 nucleate; glycogen in a dense mass; no chromatoids, *Iodamœba bütschlii*.
6. Nuclei with central granular karyosomes, and no peripheral chromatin (cysts unknown), *Dientamœba fragilis*.

Occurrence of Amœbæ in Healthy Persons.—The presence of amœbæ in the stools of apparently healthy individuals formerly inclined many authors to believe that all amœbæ were without etiological or pathological significance. Schuberg, in 1893, found amœbæ in the stools of 10 out of 20 healthy persons to whom a dose of Carlsbad salts had been given. Kruse and Pasquale, in 1894, when perfectly healthy, observed amœbæ in their own feces and in those of 38 persons either healthy or suffering with diseases other than dysentery. In 1899 Musgrave and the writer found that 4 per cent. of patients examined in the Philippines who had no dysentery or history of the disease harbored amœbæ. A dose of Rochelle salts had been given to these individuals by the mouth previously. Schaudinn found amœbæ which he considered harmless in the stools of 34 of 68 healthy people in East Prussia, in one-fifth of the cases examined in Berlin and in 256 out of 385 in Austria. The amœbæ in the human intestine which do not give rise to disease are usually of the *Entamœba coli* type, which has a wide geographical distribution. Schaudinn twice infected himself with this amœba and controlled his feces before infection for two months, to be sure that his stools were free from this organism. After infection he suffered from no intestinal disturbance. In Manila as high as 70 per cent. of healthy American soldiers were found by Ashburn and Craig to harbor *Entamœba coli*. From its frequent occurrence in healthy individuals for very long periods of time without symptoms of diarrhœa and dysentery, and from the negative results obtained in animal experiments it has generally come to be regarded as a harmless commensal of man.

Later the tendency became prevalent to classify all amœbæ found in the stools and intestines of apparently healthy individuals as *Amœba coli*. This led in turn to considerable confusion until it was recognized that there are periods in the course of amœbic enteritis, particularly in the earlier stages, in which symptoms are entirely lacking. Hence when *Entamœba histolytica* is found in the stools of healthy individuals we cannot say that they are not suffering with an early or latent form of the disease, or that the malady does not exist in its incubation period, unless we follow them over long periods of time in which no disease develops. In other cases in which infection with *Entamœba histolytica* is present, the infection may be so mild as to produce practically no symptoms unless the resistance of the patient is lowered by other intercurrent disease. It is not necessary to suppose in these cases that lesions of the intestine are always present, although in some lesions may exist which we cannot always be aware of during life.

The recognition of the *carrier condition* in amœbic dysentery, formerly observed in various other infectious diseases, has also assisted in clearing up many difficulties in understanding the nature of *Entamœba histolytica*.

Walker divided the amœbic carriers into *contact carriers* and *convalescent carriers*, the former having never suffered from amœbic dysentery, the latter having had an attack of amœbic dysentery and having recovered from a clinical standpoint, the infection with the amœba persisting. The contact carrier therefore is a healthy individual whose infection does him no appreciable harm, while the convalescent carrier constitutes an individual who has shown himself susceptible to the parasite and who continues to pass cysts of this parasite in his stools. The percentage of persons who acquire infection with *Entamœba histolytica* and subsequently become healthy carriers cannot be definitely stated. The figures of Walker and Sellards show that of 18 men experimentally infected with *Entamœba histolytica*, only 4, or 22 per cent, developed symptoms of amœbic dysentery. The remainder, 14, or 77.8 per cent., became contact carriers. Some were under observation for over two years and never showed any signs of dysentery or other symptoms attributable to the amœbæ. Wenyon and O'Connor found 106 carriers among 1979 healthy men examined in Egypt. Of these 106 infected individuals only 16 gave any history of dysentery, and they believe the latter figure too high for the diagnosis of amœbic dysentery, for in no case were they certain of the type of the disease from which the individual suffered. A few observers still incline to the belief that all amœbæ in the human intestine are or may become pathogenic. It has been noted that Stiles in an examination of over 8000 persons in different states found that 4.1 per cent. were infected with the cysts of *Entamœba histolytica*, and hence these individuals might be classified as carriers. Why a very large percentage of such individuals never suffer from intestinal disturbances is unexplained. Were it not for the fact that the cysts have been reported to be present in fairly large numbers in some instances, the idea might occur that such cysts were continually being ingested in the drinking water or in food, and had passed through the alimentary tract unchanged, either because they did not find favorable conditions for excystation or that the cysts were no longer viable.

Acton and Knowles,[1] in 1924, in India, expressed the opinion that there is reason to doubt whether the healthy carrier is always free from clinical symptoms. These observations were made in India where amœbic dysentery is very common, and are in great contrast to those observations which have been made in the northern United States and in Great Britain.[2] We know nothing as to whether the pathogenesis of some species of amœbæ under certain conditions may be increased by long periods of existence in the human intestine.

Occurrence of Amœbæ in the Stools of Those Suffering with Other Diseases than Dysentery.—Another argument advanced against the etiological significance of amœbæ in dysentery is the fact that these organisms have been found in the intestines of those suffering with other diseases, such as chronic diarrhœa, cholera, typhoid fever, etc. In many of the reported cases the chronic diarrhœa might be regarded as a symptom of pathogenic amœbic infection. But in some of these the *Entamœba coli* may

[1] *Indian Med. Gaz.*, 1924, **59**, 440.
[2] Smith, A. M.: *Brit. Med. Jour.*, 1924, p. 897.

have been the protozoön present. Kruse and Pasquale found no lesion at autopsy in some of their patients in whom amœbæ were present.

In the tropics, where amœbic dysentery is so common and frequently of long standing, concomitant occurrence with typhoid fever, cholera, bacillary dysentery or tuberculosis is not very uncommon. In the writer's series of 100 fatal cases of amœbic dysentery in soldiers there were 4 cases of concomitant infection with typhoid fever.

The Non-occurrence of Amœbæ in the Stools of Dysenteric Patients.—Many observers have advanced the argument that since amœbæ are sometimes not found in the feces or intestines of those suffering with tropical epidemic, or sporadic dysentery, these organisms are not the cause of the disease. Shiga in Japan, Flexner and the writer in the Philippines, and Leonard Rogers in India, have shown that tropical dysentery consists particularly of at least two forms, one due to a species of amœbæ and the other to a species of bacterium. These conclusions have been confirmed also for temperate climates. In addition there are a number of other forms of parasitic dysentery which may be easily recognized from the microscopic examination of the stools. Two of the commonest are due to *Balantidium coli* and *Schistosoma mansoni.*

Inoculation Experiments.—Several methods have been chiefly employed: (1) The direct injection into the rectum of feces containing the parasites. In this manner positive results have been obtained in cats, monkeys and dogs. In these experiments not all the inoculated animals became infected, and single experiments and those in which unsuitable material is employed are likely to fail. There is no doubt that lesions may be produced in the large intestine in cats by this method. (2) By feeding encysted forms of amœbæ. Cassagrandi and Barbagallo, Calandruccio and Schaudinn fed themselves encysted amœbæ, apparently of the *Entamœba coli* type, produced infection, and reobtained the amœbæ from their stools. They had no symptoms of disease following the infection. They also infected cats by feeding encysted cultures of this parasite but obtained no symptoms of disease. Upon feeding the cysts of *Entamœba histolytica* to cats Schaudinn obtained dysentery and ulceration of the large intestine in which numerous amœbæ were found. Quincke and Roos fed stools containing encysted amœbæ to two cats and obtained infection and amœbic ulceration, which they observed at autopsy. Musgrave fed encysted amœbæ in cultures with bacteria to monkeys and obtained in a small percentage of the cases, dysentery and ulcerations in which amœbæ were found.

Other observers have claimed that natural infection in the monkeys employed in these experiments was not carefully excluded. Both the lower monkeys and orangoutangs contract the disease naturally and at one time as many as 4 or 5 of our laboratory animals were suffering with naturally acquired infection. Greig and Wells[1] showed that in India natural infection in monkeys is very common; of 53 monkeys examined all showed amœbæ in the feces which appeared and reappeared at irregular intervals, so that repeated examination was sometimes neces-

[1] *Memoirs of the Sanitary Department of the Government of India*, 1911, n.s., p. 47.

sary to discover them. Some of these animals seemed perfectly healthy while others had dysenteric symptoms. Franchini[1] showed that in a healthy monkey amœbic dysentery and typical lesions may be produced by rectal injections of *Entamœba tetragena*. Ujihara has reported successful transmission of *Entamœba histolytica* from man to monkeys. Castellani[2] observed in a monkey the occurrence of amœbæ in an abscess of the liver in which no bacteria could be discovered. There were no evidences of disease in the intestine. The abscess was not produced by inoculation but occurred spontaneously. Many observers have observed amœbæ in different species of the smaller monkeys, while the writer has observed amœbæ in a fatal case of amœbic dysentery in an orangoutang, and Suldey,[3] 1924, in a fatal case of amœbic enteritis in a chimpanzee.

Kessel,[4] 1924, found monkeys of the genus *Pithecus* naturally infected with *Entamœba dysenteriæ, Endolimax nana, Councilmania lafleuri* and *Iodamœba bütchlii*. He successfully established infestation of *Pithecus* monkeys with these protozoa in animals which showed no previous infestation with them. The successful results were obtained by single feeding of 5 c.c. of diluted human feces containing the cysts of the protozoa indicated.

Werner, Darling, Fanthan and others produced dysentery in kittens by feeding the feces containing the cysts of either *Entamœba histolytica* or *tetragena*, while feeding the cysts of *Entamœba coli* to kittens has produced infection in some instances but no symptoms of dysentery. Wenyon[5] produced dysentery in kittens by inoculation of the feces, and in one instance amœbic abscess of the liver, which developed spontaneously, apparently as a result of the amœbic intestinal infection. Amœbic abscess of the liver has often been produced experimentally in cats.

Sellards and Baetjer showed that inoculation of kittens by rectum or by feeding dysenteric stools rich in amœbæ resulted in infection in about 50 per cent. of the experiments. By inoculating the material directly into the cecum they were able to infect every one of the kittens, and were also able by this method to propagate a strain of amœba through a series of animals for several months. While this method of inoculation proved to be very satisfactory in their experiments, other observers, while sometimes obtaining successful results by this method of inoculation, have at times had failures. Baetjer and Sellards and Chatton have succeeded in sometimes infecting guinea-pigs with *Entamœba histolytica*, and Huber reported the infection of rabbits, though the lesions in these animals seem to be peculiar.

Against the experiments, in which bacteria together with the amœbæ were employed, being used as an argument in favor of the pathogenesis of the parasites, objection was naturally urged. Therefore attempts were made to employ material in which amœbæ were present without microörganisms. Kartulis and Kruse and Pasquale used the contents

[1] *Centralbl. f. Bakteriol.*, 1911–1912, **41**, 590.
[2] *Parasitol.*, 1908, **1**, 101.
[3] *Bull. Soc. Path. Exot.*, 1924, **17**, 771.
[4] *Proc. Soc. Exper. Biol. and Med.*, 1924, **22**, 206.
[5] *Jour. London School Trop. Med.*, 1912, **2**, Part I.

of liver abscesses free from bacteria and produced dysentery and ulcerations in the intestines of cats by rectal injections. They stated that while the lesions in their most successful experiments bore in many points a striking resemblance to those seen in man, they were not identical. In 1899 the writer obtained dysentery and perfectly typical amœbic ulcerations in the large intestine of cats by the injection into the rectum of portions of the contents of a liver abscess which contained living amœbæ but was otherwise sterile. These lesions were *perfectly typical of the lesions seen in man.* Many of the ulcers showed a distinct undermining of the mucosa and a round-celled infiltration of the submucosa, with numerous amœbæ at the base of the ulcers. These experiments were practically conclusive of the pathogenesis of this species of amœbæ. It is possible that toxic substances may be introduced with the amœbæ in the pus of these liver abscesses, and it might be argued that these cause erosions of the mucosa. However, a chemical substance alone could hardly produce the typical anatomical lesions of the disease which are so peculiar to amœbic infection and which no one has produced without amœbæ.

Lynch, Brug, Kessel and Chiang have infected rats by feeding them stools from human beings infected with several different species of amœbæ and their cysts, and several of these observers have found rats naturally infected with the human amœbæ. Walker and Sellards performed important experiments in man in connection with infection by feeding amœbæ. They first fed cultures of amœbæ cultivated from water or other non-parasitic sources, as well as from dysenteric stools, to 10 men without producing dysentery in a single instance, or finding such amœbæ in the stools upon microscopic examination. Of 20 such experiments performed on the 10 men, in 13 they recovered amœbæ in cultures from the feces from the first to the sixth day, but never afterward. They concluded that amœbæ which can be cultivated are non-pathogenic. Twenty persons were fed with material that contained *Entamœba coli.* There was a uniform failure to recover organisms culturally from the stools and in no instance was dysentery produced, though 17 became parasitized as a result of a single feeding in from one to eleven days, the entamœba being found in the stools and persisting there for extended periods. They concluded that *Entamœba coli* is an obligate parasite, non-pathogenic, and cannot be cultured.

In another series of experiments twenty feedings were carried out with *Entamœba histolytica*, the fecal material being mixed with powdered starch or magnesium oxide and given in gelatin capsules. Seventeen men became parasitized after the first feeding, 1 required three feedings and 2 who did not become parasitized at the first feeding were held as controls. The average time for parasitization was nine days. Only 4 of the 18 parasitized men developed dysentery which came on twenty, fifty-seven, eighty-seven and ninety-five days respectively after the ingestion of the infecting material.

Source of Amœbæ and Mode of Infection. –One of the greatest sources of infection is through drinking water contaminated directly or indirectly with fecal material from cases of amœbic dysentery. Food contamin-

ated directly or indirectly, and particularly uncooked foods, such as salads, lettuce, etc., may also be a source of infection. Infection of man frequently follows upon the ingestion of the living cysts from which the amœbæ which they contain are liberated, probably under the influence of the ferments of the intestine. These cysts are formed normally in the intestine of the host who is a carrier of the infection, and are passed in his dejecta. However, the cysts may also under certain circumstances be formed outside of the human intestine. Yoshida[1] showed that encystment of the dysentery amœbæ could be observed in artificial media. In certain attempts at cultivation of amœbæ in artificial media performed by the author in 1923 in Honduras, while no cultivation of *Entamœba histolytica* was obtained, definite encystment of *Entamœba histolytica* was observed in tubes of coagulated egg medium such as has been employed for the cultivation of *Bacterium tularense*. Chiang (1925) has shown that in his cultures of *Entamœbæ*, encystment often occurs in the cultures.

Any vehicle of these cysts in a living condition to the mouth and alimentary tract of man is of importance in relation to infection. The cysts upon being passed in the dejecta must find some suitable environment to remain viable. Since they are killed by complete desiccation, dust is probably not a source of infection. In a suitable liquid or damp medium they may survive for at least two to three weeks in water, and sometimes for the same period in moist feces particularly if they are kept cool.

It has also been demonstrated that certain flies which have fed on infected feces will ingest the cysts and later deposit them unaltered in their excreta. Stiles and Keister, Wenyon and O'Connor, Root[2] and others have shown that flies may be important factors in the spread of intestinal protozoa. Wenyon and O'Connor found the cysts of *Endamœba histolytica* in wild flies caught at random. Buxton found cysts of *Entamœba histolytica* in 0.3 per cent. of the house flies caught in Mesopotamia. According to Wenyon and O'Connor the cysts may appear in the excreta of the flies as early as five minutes and remain there viable as long as twenty-four hours after feeding, and in exceptional instances for as long as forty-two hours if the fly is not fed in the interval.

Roubaud found that cysts of *Entamœba coli* and *Entamœba histolytica* traverse the digestive tract of flies and are passed unaltered with the fly's feces. He found these cysts in the feces for over twenty-four hours, but only rarely after forty hours. If the fly which had ingested cysts was drowned in water the cysts might live for a week. Root found that free forms of *Entamœba histolytica* which were ingested by flies were killed in an hour or less if they did not become encysted. In the case of *Entamœba histolytica* the cysts after being ingested by flies were found to live as long as forty-nine hours, in the case of *Entamœba coli* as long as fifty-two hours. When the flies which had ingested cysts were drowned in water some of the cysts of *Entamœba histolytica* appeared to be viable as long as seven days. Kuenen and Swellengrebel showed that flies

[1] *Jour. Exp. Med.*, 1918, **28**, 387.
[2] *Am. Jour. Hyg.*, 1921, **1**, 131.

might carry on their surface living cysts of the amœbæ, but these cysts did not survive on the surface of the flies for longer than about one hour. If the cysts in the fly droppings are deposited upon a moist medium, such as certain varieties of food, flies obviously constitute another means of carrying the infection.

The cysts are formed normally in the intestine of man who constitutes a carrier of amœbic infection, and the vegetative forms may also sometimes undergo encystation outside of the human body. An individual who constitutes a carrier and passes these cysts in the stools may never have suffered from any disturbances due to this infection, or he may be a patient who has partially or wholly recovered from amœbic enteritis or dysentery. We do not know exactly what condition in the intestine causes the amœbæ sometimes to encyst, but we suppose that they do so under certain conditions which are unfavorable for the vegetative stages of their growth. While man usually becomes infected by swallowing the cysts of amœbæ, it is by no means certain that he may not sometimes become infected from swallowing in large numbers the vegetative forms which have passed under certain conditions unchanged through the stomach into the intestine. In fact, Walker produced amœbic infection in 2 men by feeding them portions of the stool of a man suffering with an acute attack of amœbic dysentery containing motile *Entamœba histolytica*. In view of these facts, and because encystation may occur outside of the intestine, it would be dangerous to assume, as has been done by one author, that the patient with acute amœbic dysentery is unable to transmit his infection to other individuals and does not constitute a source of infection. Some years ago the writer called attention to the danger of the spread of amœbic infection in the tropics by monkeys whose dejecta contained *Entamœbæ*. These animals may pollute water supplies, particularly where rain water is used for drinking purposes and is stored in uncovered receptacles. While sporadic cases of entamœbic dysentery have been reported in dogs, and cats may be artificially infected, it is not probable that these animals play an important part in the spread of the human infection. Franchini is apparently the only author who appears to hold the view that cats may be an important source of infection for man. Cysts have not been reported as occurring in the stools of cats.

Lynch found wild rats in Charleston, South Carolina, affected with amœbic ulcerative colitis, and produced this disease in rats by feeding them human feces containing amœbæ, both in the active and resting stage. He believes the organism in the rat to be *Entamœba histolytica*, and suggests that amœbic dysentery may be sometimes caused in man by the ingestion of food soiled with the excrement of infected rats. Wenyon states that he knows of no method of distinguishing the amœbæ of the rat from *Entamœba coli* of man, but he does not explain the ulcerative amœbic dysentery which Lynch observed in the rat.

Lynch's work has been confirmed by Brug, Kessel and Chiang. Brug found *Entamœba histolytica* in wild rats in Java, and succeeded in infecting a rat experimentally by feeding it upon cysts from human feces.

Kessel,[1] in 1923, reported that infections of five species of human intestinal amœbæ (*Endamœba dysenteriæ, Entamœba coli, Councilmania lafleuri, Endolimax nana* and *Iodamœba bütschlii*) have been experimentally transferred to rats which were primarily amœbæ free, by feeding them human feces containing cysts of these amœbæ. Infections of *Entamœba dysenteriæ* and *Councilmania lafleuri* have been experimentally transferred to mice. One of the 4 rats that died infected with *Entamœba dysenteriæ* showed an intestinal ulcer. The cysts and motile forms of the amœbæ were recovered without any apparent morphological change in the infected animals. He concludes that heavy suspicion is thrown on the rat and mouse as possible carriers of the causative organisms of human amœbiasis.

Chiang,[2] in 1925, found normal laboratory rats infected with *Endamœba histolytica* and two other species of amœbæ. He infected normal laboratory rats with *Endamœba histolytica* obtained from man. While the rats themselves so infected did not suffer from dysentery, this same amœba when injected into kittens sometimes produced definite dysentery lesions. Sixty-two per cent. of the kittens were actually infected with amœbæ from the rat and 1 animal showed definite lesions.

In the Philippine Islands it has been noticed that sometimes a heavy rainfall will increase markedly the number of cases of amœbic dysentery in a district. Such increase is probably caused sometimes from the surface infection of wells and water supplies, by the washing out of cesspools and other places contaminated with human fecal material. In Egypt there is an increase of the disease at the time of the annual overflow of the Nile, which probably results from a similar cause. While the amœbæ that are found almost constantly in the water supplies in some tropical countries are usually of the free-living type, and apparently non-pathogenic for man, it is premature to conclude that such waters which contain vegetative forms of amœbæ in large numbers are pure, and such water supplies should be regarded as unsafe for drinking purposes unless sterilized. For we have not the evidence to show that some of these amœbæ may not under certain conditions and after encystment be or become pathogenic for man.

Infection with *Entamœba histolytica* may persist in many instances for long periods of time after the symptoms have subsided, during which time the encysted *entamœbæ* may be passed in the stools and constitute an important source of infection to other individuals. Attention has been called to the presence of cysts of *Entamœba histolytica* in the feces of healthy individuals who constitute amœbæ carriers and many of these individuals have never suffered from intestinal disturbance. It is the consensus of opinion that amœbic dysentery is at least generally only spread by the carriage of the cysts from the feces to the food and drink of individuals. If the human or animal excreta containing the cysts come into contact with food and drink human infection may occur, and such infection is particularly likely to occur in districts in which the

[1] *Proc. Soc. Exper. Biol. and Med.*, 1923, **21**, 110.
[2] *Proc. Nat. Acad. Sci.*, 1925, **11**, 239.

proper or sanitary disposal of excrement is not carried out, or where surface privies are in use in which the excreta are exposed to flies.

Other Organisms in Amœbic Dysentery.—Other protozoal organisms common in the intestine in amœbic dysentery are the *Chilomastix mesnili*, *Trichomonas confusa* and *Giardia lamblia*. These, when present in very large numbers, probably by their rapid mechanical movements, act as an irritant to the already inflamed mucosa. Occasionally *Spironema curyyyrata* may be present in large numbers, particularly if the stools are diarrhœal in character. Very rarely infection with the *Coccidia*, *Isospora* or *Eimeria* may occur. The yeast-like organism, *Blastocystis hominis*, is not infrequently found in stools in the tropics, and may cause some confusion as it sometimes resembles the cyst of amœbæ. Kessel[1] reported the presence of *Trichomonas hominis* in the pus of an amœbic abscess of the liver. Other animal parasites found not infrequently in the intestine of those who suffer with amœbic dysentery in the tropics are the *Tænia saginata*, *Ascaris lumbricoides*, the *Trichuris trichiura*, *Uncinaria duodenale*, *Ankylostoma americanum*, *Strongyloides intestinalis* and *Oxyuris vermicularis*. *Balantidium coli* may likewise be present and give rise to intestinal lesions. In some countries the ova of *Schistosoma mansoni* and *Schistosoma japonicum* may be found in the stools. When these parasites are present the cases may be regarded as those of multiple infection. In some instances *Bacillus dysenteriæ*, *Spirillum choleræ* and *Bacillus typhosus* have been isolated from the stools in cases of amœbic dysentery.

Bacteriology.—Kruse and Pasquale investigated the organisms found in 14 cases of the disease and isolated streptococci, *Staphylococcus pyogenes*, typhoid-like bacilli, *Bacillus pyocyaneus* and *Bacillus clavatus*. None was present so constantly or in such numbers as to suggest a specific relation to the disease. In 26 of my fatal cases in plate cultures from the large intestine several varieties of the colon bacillus were the only organisms found constantly present. We were unable to produce dysentery or any lesions in cats by rectal injection of cultures of the varieties of the colon bacillus encountered. In 76 fatal cases cultures were made from the solid organs. The bacteria encountered were streptococci and staphylococci, *Diplococcus pneumoniæ*, colon bacilli, the typhoid bacillus and *Bacillus aërogenes capsulatus*. The most striking fact demonstrated was that 5 per cent. of the cases succumbed from a general terminal infection with the *Staphylococcus* and *Streptococcus pyogenes*.

Pathology.—The Large Intestine.—The large intestine is chiefly involved. One of the most striking features in chronic cases is the great thickening of its walls. This may be confined to the submucosa or involve all the coats. It is always more marked in the submucosa and is due to a general œdema and localized areas of thickening. The other characteristic lesions consist chiefly of hemorrhagic catarrh, of raised hemispherical areas of infiltration protruding above the level of the surrounding mucosa, often surrounded by zones of hyperemia and

[1] *Jour. Parasitol.*, 1925, **11**, 151.

hemorrhage, and of ulcerations which vary considerably in different cases. At least three forms of ulceration are common. Frequently a diphtheritic process is added to the amœbic one. The lesions may affect the whole large intestine or a portion only, as the cecum, the hepatic or sigmoid flexure, or the rectum. Generally in fatal cases the large bowel is affected throughout. In some the intestine is riddled with ulcers; in others a moderate number are scattered through it. There appears to be no particular portion of the large intestine that is definitely predisposed to the infection, though the cecum shows ulceration somewhat more frequently than other portions in fatal cases.

The amœba insert themselves either between the cells of the normal mucosa, along the interglandular substance, or into small erosions which may exist in the intestine from other causes. They next generally work their way through the muscularis mucosæ by the lymph channels and finally enter the submucosa. Here migration and reproduction take place and infiltration with round cells and œdema result. The mucosa becomes bulged out and small pinhead-sized dots appear on the interior of the bowel. Should a small capillary hemorrhage result in these areas, as frequently happens, the nourishment of the overlying epithelial cells becomes disturbed, and these, perhaps partly by digestion, become gradually disintegrated, softened and cast off. The œdematous submucosa is then exposed, which may appear yellowish from infiltration, with round cells or yellowish-red if the blood cells still remain in this area. Thus the earliest erosion is formed and becoming exposed to fecal material and bacteria, an increased number of cells accumulate, and if pus cocci are present more or less true suppuration occurs.

The process is limited in extent by the surrounding tissue, which is well supplied with blood and hence red margins to the erosions or ulcerations exist. The amœbæ on the surface die or are cast off into the lumen of the intestine, but others migrate deeper and laterally into the submucosa. Should no hemorrhage occur early beneath the small bulgings of the mucosa, the areas increase in size through the œdema and round-celled infiltration; hence the diameter of these erosions and small ulcerations when first seen depend upon how long the overlying mucosa remains intact before becoming necrotic, disintegrated, and cast off. They therefore generally vary in size from 2 or 3 mm. to about 2 cm. In many of the ulcerations that have originated from nodules which reached 1 or 2 cm. or more in size before opening, we may see evidences of the primary nodular formation from the fact that the margins are raised and thickened and in many cases undermined. Some of the ulcers have a distinct crater-like appearance, with a small opening in the centre, which may be pinhead in size or so large as to freely expose the cavity. The mucosa between the ulcers in early cases may appear perfectly normal, but in later ones a desquamative or hemorrhagic catarrh may be present. The ulcerations increase in size, probably owing to the combined action of both amœbæ and bacteria. The floors and edges become softened, necrotic and covered with a mucous exudate. In the earlier stages the ulcers are round or oval and placed with their long diameters transversely to the lumen of the intestine. Later they may

FIG. 26.

Colon in amœbic dysentery.

FIG. 27.

Colon in amœbic dysentery.

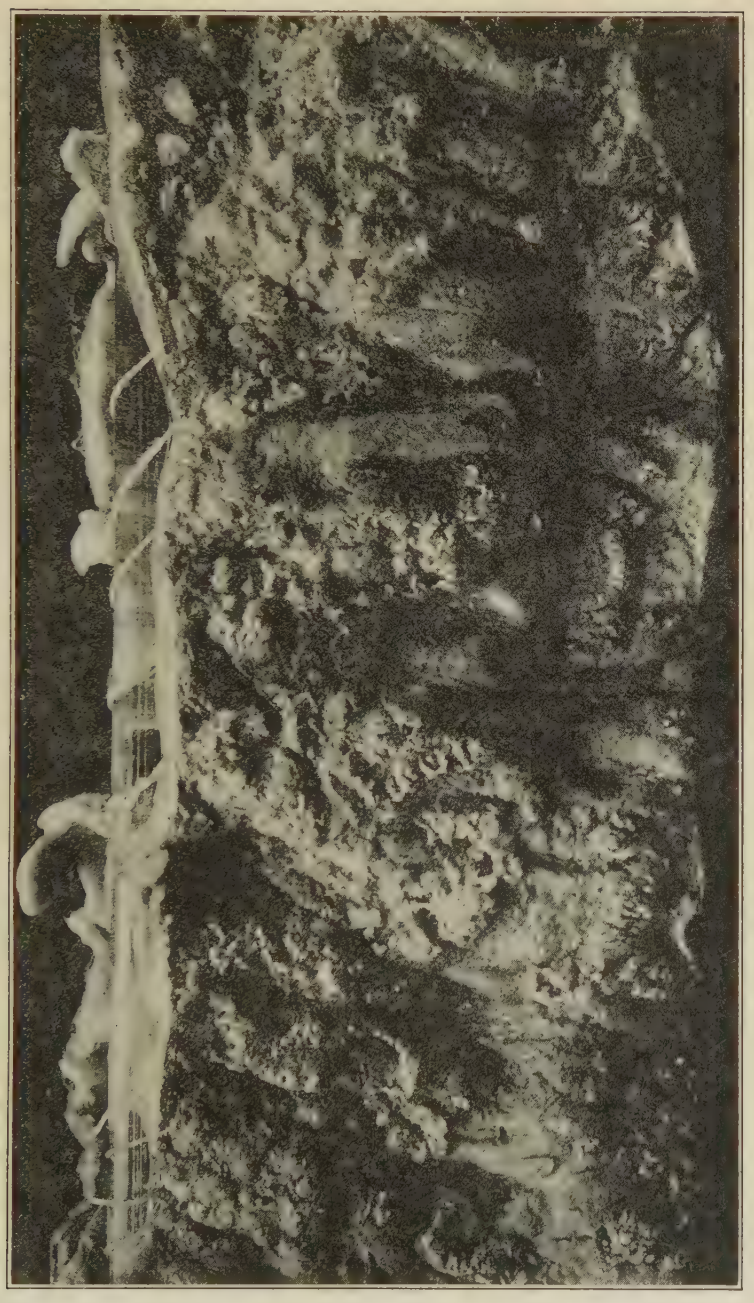


Fig. 28. Colon in amœbic dysentery.

become irregular in outline. The diameter of the large ones probably depends chiefly upon how laterally the amœbæ have spread out in the submucosa, and their depth mainly upon the depth the amœbæ have penetrated into it before the overlying mucosa was cast off. In the more serious lesions extensive surface ulcerations result whose floors are formed usually of submucosa or deeper ones with smaller diameters whose bases consist of submucosa, muscular coat or even peritoneum. It is in the ulcerations of moderate depth, owing to the burrowing of the amœbæ in the submucosa beneath the mucosa, that the characteristic undermining of the borders of the ulcers results. This becomes particularly marked owing to the fact that the muscularis mucosæ are not infiltrated and destroyed to the same extent as the submucosa and hence holds up the mucous membrane. Some of these large ulcers are often formed by the coalescing of smaller neighboring ulcers through sinus communications formed in the submucosa, the overlying muscularis and mucosa then sloughing off.

Another form of ulceration sometimes seen is that in which the lesion extends only partially through the mucosa and results from a gradual disintegration of the epithelial cells and not by necrosis and sloughing of the underlying tissues. The bloodvessels of the mucosa are likely here to be more dilated and filled with blood. These ulcers may develop both laterally in the mucosa and in depth into the submucosa; but there is not in either case the characteristic undermining observed in ulcerations of the other type, though the round-celled infiltration in the vicinity is frequently even more extensive. When these surface ulcers extend only into the mucous membrane amœbæ are rarely found in them, but they are sometimes encountered at their margins lying in or between the glands. It seems probable that this form is a direct extension into the mucosa of the process which begins as a hemorrhagic catarrh. It may be due to the action of soluble toxic products of the amœbæ aided later by the intestinal bacteria. A somewhat similar process is observed in the liver, which consists of an extensive necrosis of areas of liver tissue which contain no amœbæ and which are situated in the vicinity of the abscess. Complete breaking down and softening seem to occur only when the amœbæ actually come in contact with the cells, and this may be due to the action of an intracellular toxin or ferment.

The amœbæ wandering in the submucosa and carrying with them adherent bacteria cause continuous disturbance. The parasites themselves seem to be responsible chiefly for the œdema and round-celled infiltration, the softening, liquefaction and breaking down of the tissues. The bacteria cause additional leukocytic infiltration and necrosis. The action of the latter is manifested chiefly in the more superficial ulcerations where the amœbæ may be scanty upon the surface. The parasites in addition cause early infiltration with round cells of the walls of the capillaries and veins, followed by softening and complete disorganization of these structures. It is in this way that much blood appears in the stools. The amœbæ may penetrate the walls of the veins, and are frequently found inside these vessels, some of which they may have entered directly or been carried from the capillaries through the lumen

of the vessel. In some instances they cause thrombosis of the blood-vessels of the submucosa or muscularis with consequent necrosis of the tissues above. MacCallum has observed the amœbæ underneath the endothelium of the branches of the portal vein as well as lying free in the lumen of such venules.

In certain cases the tissues seem little able to resist the infection, and large gangrenous ulcers result, the walls of which are soft and the bases of which are formed of blackish or greenish, sloughing tissue in which numerous cocci, bacilli and sometimes amœbæ are found. These changes are certainly not produced entirely by amœbæ, but are probably due chiefly to bacteria. Another process is the diphtheritic one, also certainly partially if not entirely caused by bacteria.

The process of healing may best be studied in patients who have been under treatment for some time and in whom death has resulted suddenly from some complication. The ulcers may then be found with bases which are distinctly depressed and have a grayish or grayish-yellow color. Their margins, however, are raised above the bases, and are clear cut but are not usually swollen above the surrounding mucosa. When well advanced toward healing they are no longer softened. The surfaces of the ulcers are bathed in a serous fluid or covered with mucus. Healing takes place by the formation of fibrous connective tissue in the floors and by a gradual covering over with epithelium. If the lesions have been extensive old pigmented scars result.

Peritonitis.—The amœbæ may wander freely through the submucosa and into the circular muscular coat, where they are frequently found along the intermuscular septa and between the muscle fibres, which they have evidently separated. The fibres themselves become swollen, granular, indistinct and may appear without nuclei. They finally become infiltrated, break up and disappear. The parasites also destroy the bloodvessels in this layer; the blood supply is then cut off and more extensive sloughs are formed. They may next push along the intermuscular septa through the longitudinal muscle and produce the same changes. Should they approach the serosa similar changes to those seen in the submucosa take place in the subperitoneal coat.

In case many bacteria, particularly the pus cocci, now find their way into the tissue, deep, sloughing, gangrenous lesions are formed and perforation with general peritonitis frequently occurs. In other cases when few bacteria are present this may take place from violent peristalsis after adhesions are formed. However, in the latter instance, particularly when the floor of the ulcer is composed of muscular tissue and does not extend completely down to the serosa, the peritoneal coat, owing to the action of the amœbæ, becomes greatly thickened, not only from the œdema and infiltration but by the formation of considerable fibrin. Occasionally general peritonitis will occur with no visible perforation, the amœbæ having penetrated the muscular coat and serosa and set up an inflammatory exudate which consists of an opaque gelatinous fibrinous fluid in which the amœbæ may be found.

Microscopical Features.—The accumulations of amœbæ in the submucosa where there is no ulceration are attended by a low grade of

inflammatory reaction, with œdema, lymphocytic infiltration and fixed tissue proliferation. The amœbæ are particularly found in the œdematous tissue beyond the areas of most acute inflammation in which the intestinal bacteria also are encountered and play a part.

One of the most striking points is the absence of the usual products of purulent inflammation. Polymorphonuclear leukocytes are found in relatively small numbers in the tissues, and are never aggregated together in large groups unless many bacteria are present. The submucosa is very œdematous. Its interstices are widened and the lymph channels engorged. In addition, there may be a general liquefaction of the tissues. Extensive round-celled infiltration exists in the submucosa where but few polymorphonuclear leukocytes are usually seen. Plasma cells are present at times in considerable numbers, and eosinophiles are in some cases also fairly numerous. The amœbæ are found in large numbers in the lymph spaces, in which case the endothelial cells in the neighborhood are proliferated and there is sometimes a fibrinous exudate inside the vessel. The parasites are also present in the ulcers, being most numerous in the submucosa along their bases and sides, in the zone of œdema and round-celled infiltration which borders the necrotic portion of the lesion.

Involvement of the lower end of the *ileum* sometimes follows from an extension of the process upward from the cecum. The mucosa just above the valve is frequently hyperemic and occasionally hemorrhagic. In one of the writer's autopsy series did it show amœbic ulceration.

Lymphatic Glands.—The mesocolic glands are frequently swollen, particularly where the lesions are extensive and extend deeply into the muscular coats. They may occasionally be hyperemic or œdematous but are very rarely hemorrhagic, and in this respect offer a strong contrast to the condition of the lymphatics in bacillary dysentery. The lymph sinuses are more or less dilated, and there may be some proliferation of the connective-tissue cells and a few plasma cells present. In rare cases necrosis may take place and bacteria may be present.

The chronic cases sometimes show evidence of parenchymatous *nephritis*, which is rarely of extreme grade. The *spleen* and the *heart* muscles are usually normal, and the *lungs* show no special changes peculiar to the disease except abscess of the right lower lobe. Abscess of the brain and spleen may also occur.

Symptoms.—These may vary so widely that in order to discuss the subject intelligently the cases may be grouped for convenience under the following divisions: (*a*) Mild, or latent forms; (*b*) cases with acute onset; (*c*) advanced and chronic forms. This division is purely arbitrary since no sharp lines of distinction can be drawn and the cases may pass from one to the other. Moreover, instances may occur which can be better considered partially under more than one of these divisions. While individual cases may vary widely there are some features which are common in at least the majority. These are the irregular course, marked by periods of intermission and exacerbation, the appearance of mucus in the stools and the tendency to chronicity. A peculiar phenomenon is the frequent occurrence of the amœbic liver abscess.

(*a*) *Mild or Latent Forms.*—Usually the patients are not able to tell exactly when they began to realize that they were not in good health. There may be complaint of some lassitude, of becoming easily tired, or of continuous slight headache; more or less indefinite abdominal discomfort and dyspepsia may be present. Slight intestinal disturbances consisting of moderate diarrhœa or of constipation may appear. Such symptoms may occur singly or in various combinations and are found in patients who, frequently in the tropics among the better classes of people, consult the physician for such minor ailments and generally have no idea of the real trouble. These vague symptoms may continue for months, and one may doubt whether they are all dependent upon the intestinal infection. When the lesions are limited to the cecum and ascending colon, dysenteric symptoms are often not present. Some of these cases which remain undiagnosed may later develop severe complications, as liver abscess, etc. Occasionally the abdominal pains become severe or there may be an outbreak of diarrhœa which causes the physician to examine the stools, when amœbæ, sometimes mucus and even red blood cells are found. A great many of these infections remain undiscovered for a long time, and may be referred to as latent or masked forms of the disease. Robust men may have the disease for a month or two without being aware that they are suffering from a serious malady. Indeed, some of the cases at autopsy show advanced intestinal lesions when the symptoms had not been sufficiently prominent to attract attention. The infection may never advance beyond this latent stage; either under simple treatment or even without treatment, the patient may overcome the infection and the parasite disappear from the stools, or the patient may remain a carrier for a long period, passing amœbæ or cysts in the dejecta. In by far the greater number, however, if pathogenic amœbæ are present some of the symptoms sooner or later increase in severity, and in the event of recovery not taking place the disease may pass to a more advanced stage. The two symptoms most likely to attract attention are *diarrhœa* and *abdominal pain*. In those patients who are constipated the latter may be the first symptom; or indigestion and gradual loss of weight may be equally prominent. Palpation of the abdomen sometimes reveals tenderness, but this is by no means constant. As the lesions in the large bowel increase, the symptoms of intestinal disturbance usually become more marked, abdominal soreness appears and the stools become more frequent and contain mucus and even blood. If they are properly treated the disease does not usually progress to the chronic stage, and this particularly is why the name "dysentery" is not an entirely apt one for the malady and why "amœbic enteritis or colitis" would perhaps answer better. The term amœbiasis, or, more correctly, entamœbiasis, has been proposed to cover all grades of the infection. Sometimes the abdominal manifestations are so insignificant as entirely to escape notice, or the appearance of a liver abscess first attracts attention.

(*b*) *Cases with Acute Onset.*—In about one-half of the cases the onset is acute. Obviously it is not correct to consider all of these as acute cases. Some are really acute almost from the beginning, but others

may have existed for some time as latent, mild or moderately severe infections. The symptoms are frequently not in accord with the lesions; ulcerations may exist and become well-marked before there is a sudden outbreak of the diarrhœa. Very abrupt onset may occur from the formation throughout the large intestine, but particularly in its lower portion, of very numerous small and superficial ulcerations, or from secondary infection with streptococci or *Bacillus dysenteriæ*. Cases with diphtheritic or gangrenous lesions may be classified clinically under this division, and in the latter instance portions of sloughing tissue may be passed in the stools. Headache, nausea and chills may usher in the attack. Soon afterward spasms of gripping pain are felt in the abdomen followed by frequent loose movements. At the onset there may be from fifteen to fifty or more bloody mucous movements in twenty-four hours. A high leukocytosis is frequently present. Colicky pains in the abdomen with rectal and vesical tenesmus occur. The pain in the abdomen is usually intermittent and acute, being most severe in the umbilical region, but later it usually becomes dull and continuous, and it is then referred to the sigmoid area. Fever, nausea and vomiting may appear; great exhaustion sets in; the heart action becomes feeble and death results from cardiac failure and collapse, or the condition temporarily improves or gradually assumes the chronic form. It is in this acute form that wild delirium may appear before death.

(*c*) *Advanced and Chronic Cases.*—In the advanced stages the symptoms become well developed. The movements become more frequent and usually contain much mucus and frequently blood. Their number may vary from two or three in the morning to ten or fifteen or more during the day. There is aching in the back, and at times sudden and intense desire to defecate. As the disease becomes chronic, loss of weight is progressive, and finally marked emaciation may result. The patient becomes anemic and the muscles soft; the tongue is pale and moist at first, later slightly furred, or sometimes heavily coated. There is more or less anorexia; indigestion and flatulence are common. The pulse and respirations may be slightly elevated in the afternoon. As the malady progresses the anemia becomes more marked, the skin dry and dull yellow in color and the face drawn. The emaciation in some cases becomes very extreme; the abdomen becomes sunken, bed-sores may appear and death follows from exhaustion or terminal infections. Another type of the chronic form is that in which there is nothing more than an intermittent diarrhœa often alternating with constipation, and accompanied usually by slow but gradual loss of flesh. These patients sometimes remain in this condition for several years. Occasionally the parasites disappear and the more serious lesions heal, but the bowel never assumes again its normal condition. Where the destruction of tissue has been extreme cicatrices form and a chronic catarrh remains.

The *course* is very variable and is not self-limited, although the increased employment of emetine in the treatment of amœbic dysentery has often greatly modified its clinical aspects, the grave cases with acute onset may terminate fatally within a week or ten days in spite of all treatment. The mild and moderately severe ones may continue for many months

before alarming symptoms appear. The occurrence of complications may terminate in death or completely alter the course. If proper treatment is instituted many of the mild and moderately severe cases recover entirely, and the parasites disappear within one to two weeks. Some of the chronic ones are completely restored to health within two or three weeks, but, on the other hand, convalescence may be delayed for longer periods. Occasionally amœbæ persist after all symptoms and sometimes the lesions themselves have disappeared; the cysts also may persist for long periods after convalescence. Complete recovery is sometimes doubtful owing to the fact that after many weeks of apparent cure a relapse may occur and the patients may develop more acute symptoms; sometimes these represent fresh infection, but usually they are merely evidences of the outbreak of the original disease. Cases of this nature, unless treatment is pursued until complete recovery results, are apt to suffer repeatedly with so-called relapses until some grave complication carries them off.

Death may occur from the gravity of the intestinal lesions, from exhaustion in protracted cases, from severe complications, from a terminal infection, from intercurrent diseases, or from severe intestinal hemorrhage. The severity of the intestinal lesions and abscess of the liver are the most frequent causes of death.

Gastro-intestinal Symptoms.—Of these, diarrhœa is the most important, usually being intermittent, coming on abruptly, and subsiding in like manner. Between the attacks the stools may become formed. The intermissions may last several weeks or even months, or diarrhœa may be absent throughout the entire course. The character of the diarrhœa usually depends upon: (1) The ulceration, whereby increased peristalsis results, probably owing to the nerves being eroded and exposed; (2) the impaired power of absorption of water by the intestine, due in part to the marked œdema. Ulcers of the intestine can exist without any diarrhœa resulting, as is particularly likely when the ulcers are superficial and in the cecum or the adjacent portion of the ascending colon. When the ulcers are very numerous throughout the intestine, or well developed in the descending colon and rectum, diarrhœa is practically always present. In mild cases the movements may not exceed three or four in twenty-four hours, but in the gangrenous and diphtheritic forms the diarrhœa becomes excessive and the movements sometimes number fifty or more in this time. In fatal cases before death they may diminish to two or three. This has been explained as due to the gradual loss of expulsive power caused by the destruction of the muscular coat and nerves situated in the ulcerated areas, and the general œdema of the bowel wall.

Feces.—The stools vary greatly in different stages and in different cases. Valuable information may be obtained from them of the condition of the lesions in the intestine and of the progress of the disease. At times they are liquid, at times pultaceous and again well formed. In color they may be brownish, greenish, reddish, grayish, or variegated. In cases with gradual onset they are likely at first to be merely more or less watery and of normal color. As the lesions develop, mucus begins

to appear. In the cases with marked intestinal catarrh and extensive ulceration it is always more abundant. The mucus may be finely divided, shreddy and mixed throughout the stool, or it may appear in large masses. The latter condition is particularly likely to exist when the feces are well formed, when small portions of blood-stained mucus may be observed over the surface of different portions of the stool. At times the movements consist of masses of blood-stained mucus.

Blood may be present so that the color of the whole mass is modified, or as clotted masses in portions of the stool, or mixed with mucus. It is sometimes in such small amounts as to be apparent only upon microscopic examination; or the stool may consist entirely of blood mixed with mucus. The amount of blood is partially dependent upon the rapidity with which the lesions are forming as well as upon their position and extent. The presence of considerable blood in the stool makes the diagnosis of ulceration very probable; but we cannot conclude in its absence that ulcerations do not exist. When the ulcerations are high up in the cecum the blood is apt to be altered and brownish or even blackish in color.

Polymorphonuclear leukocytes are not generally present in the stools in great numbers. They are found chiefly after ulceration is well developed and in the diphtheritic form of the disease where bacteria complicate the infection. In the chronic cases it is not unusual to find large numbers of polymorphonuclear leukocytes. Small round cells and endothelial leukocytes are usually very abundant where a well-developed catarrhal condition exists and where epithelial cells are also numerous. When pus is found in considerable amount it is an almost certain indication of extensive ulceration.

Shreds of Tissue.—As ulceration advances and becomes more chronic the amount of blood grows less; the stools become more copious and again more watery; fragments of tissue are frequently seen in the early stages of the chronic cases. In advanced and particularly in gangrenous cases large sloughs and sometimes complete moulds of the intestine are cast off.

The reaction of the stools is generally alkaline, sometimes neutral and occasionally acid. In instances of recovery the mucus is the last abnormal element to disappear from the feces. It usually persists for a long period and in many cases it never disappears.

Microscopic examination reveals the amœbæ in addition to those elements which have been described. These may be very plentiful or scarce, the number depending upon several factors. If there are only a few ulcers in the large intestine the mucus and feces that have come in contact with these lesions are likely to contain the parasites in the largest number, and they will probably be scanty elsewhere. If the stool is liquid the organisms will be more or less evenly diffused throughout. The gravity of the lesion is not always indicated by the number of amœbæ found. With very advanced lesions when the parasites are burrowing deep in the submucosa there may not be as many as in more acute conditions. Numerous epithelial cells, small round cells, endothelial leukocytes, eosinophiles and a fair number of Charcot-Leyden crystals are

frequently found. Bacteria are usually increased beyond those in normal stools.

Abdominal Pain.—This is very variable and occurs more acutely in the gangrenous cases and when perforation is imminent. It may be colicky and very severe, localized over a particular ulcer, or exist over the abdomen generally. In chronic cases a dull aching pain with occasional sharp exacerbations may be present. When this is constant, limited to a fixed point, and increased by external pressure, it is suggestive of the site of ulceration, although extensive ulceration may exist without any pain. Pain produced only by external palpation and pressure suggests areas of circumscribed peritonitis. Very excessive pain on pressure is usually present when the serosa itself is involved. If widespread or extensive ulcerations are present pain on pressure may be elicited along the whole course of the large intestine. Cramp-like and aching pains frequently occur before and after evacuation of the bowel. A feeling of abdominal heaviness is not uncommon and is frequently accompanied by distention and flatulence. *Tenesmus* is not nearly so marked or frequent in uncomplicated amœbic dysentery as in the bacillary form. It is most evident in the grave cases and in the gangrenous and diphtheritic forms, where the sigmoid flexure and rectum are involved. In the remaining cases it depends chiefly upon the extent of the ulceration in the rectum. A burning sensation in the anus after defecation is frequently present.

Nausea and vomiting of severe grade are somewhat rare but may occur early in the cases with acute onset. In moderate form they are most commonly encountered in the chronic ones. Nausea sometimes developed as a result of treatment with ipecac or of the large enemas administered for treatment.

Loss of appetite is a common symptom and is almost absolute in the acute cases. In the moderately severe ones it may not be apparent, but it becomes very evident again in the chronic cases.

Hiccough is seen in the grave forms shortly before death and when the peritoneum is involved. The *tongue* shows nothing that is characteristic. In instances of very long standing it is likely to become fissured and to show small hemorrhages and erosions along its sides and tip.

Blood.—*Anemia* of a secondary type is present in all the cases of long standing and is progressive with the disease. It is dependent chiefly upon the loss of blood from the intestinal lesions and the gastro-intestinal disturbances. It is possible that it may be in part of toxic origin due to absorption. The reduction in hemoglobin is usually greater than that of the number of the red cells; the hemoglobin varies generally from 50 to 80 per cent. Futcher's average for the red cells in 38 cases was 4,802,000. In the tropics in the advanced and chronic cases the red blood cells sometimes are not over 2,500,000. There is frequently a slight leukocytosis, and a marked one is sometimes found in the very severe cases when the polymorphonuclear cells are usually increased. The eosinophiles are not increased in cases uncomplicated with other intestinal parasites. Vaccarezza reports blood counts in 25 cases, of which 8 showed 6000 to 8000 leukocytes, 10 from 9000 to 12,000, 5 from

12,000 to 18,000 and 2 from 18,000 to 24,000; the polymorphonuclears averaged 63.48 per cent.; the eosinophiles, 3.96 per cent.

The *skin* is normal in the mild and moderately severe cases. In the chronic ones it becomes dry and sometimes glazed, and assumes a sallow, yellow appearance when the mucous membranes show distinct pallor.

Fever.—Fever is not a marked feature in uncomplicated amœbic dysentery. The temperature is likely to be elevated in the cases with acute onset; it is generally higher in the diphtheritic form, and particularly when complicated with *Bacillus dysenteriæ*. In the mild and moderately severe types there is usually little or no fever. In the chronic ones the temperature is frequently subnormal for a portion of the day, occasionally with afternoon rises of 100° to 102° F. At other times it may be subnormal or normal for a week or more. In cases with many streptococci in the stools and advanced lesions of the intestine, it may become septic with daily rises to 103° to 104° F. Fever is important in perforation and in abscess of the liver and lung, when it is sometimes accompanied by rigors and sweating.

The *pulse* and *respiration* are apt to be increased if fever is present. The pulse is frequently rapid in the grave cases with acute onset, and may become thready and rise to 120 to 140 or more. Usually in cases of moderate severity it is not over 100, and in the mild and chronic cases it may be normal. The respirations are increased particularly in abscess of the liver and lung.

Urine.—The urine is generally normal. Moderate albuminuria accompanied by a few hyaline casts is occasionally seen in chronic cases. Harris noted that in the severe forms the chlorides are often diminished and that in most severe instances they may be entirely absent. Retention sometimes occurs when acute symptoms of dysentery are present.

Complications.—Abscess of the Liver.—This is the most frequent and one of the most serious complications. In 119 cases reported by Futcher it occurred in 22 per cent.; in a series of 100 cases examined at autopsy by Musgrave and the writer, in 23 per cent.; in 74 by Craig, 33 per cent.; in 57 by Kruse and Pasquale, 11 per cent.; in 95 by Harris, 15 per cent. In India, in the British Army, Rogers found 1 case of liver abscess to every 7 of dysentery. It is much more common in males than in females. Rouis, in Algiers, found that of 258 cases, 3 per cent. occurred in women. The Indian statistics regarding families connected with the army gave a sex ratio of about 7 males to 1 female. Futcher reported 3 cases in women in his series. Natives in the tropics are much less liable to infection than Europeans. Havelock Charles[1] found that in India the death-rate from liver abscess was twenty-one times higher in British troops than in the native army. Rogers found the condition more common in Europeans than in natives in India. It is generally a complication of adult age. In the series of 28 cases reported by MacCallum[2] none of the cases occurred in individuals under twenty-one years of age. Rogers found no European patient, and in natives only 0.6 per

[1] *Brit. Med. Jour.*, 1908, ii, 1235.
[2] *Mense, Handb. d. Tropenkrankh.*, vol. **3**, 22.

cent. under ten years of age. This complication is more common in the third and fourth decades.

This complication may develop at any time and not uncommonly after all symptoms of dysentery have ceased, or indeed, sometimes before any intestinal ones have developed. In some of the fatal cases there have been no evidences of intestinal lesions and no history of dysentery. However, a history of dysentery may be obtained according to different statistics in from 60 to 90 per cent. of liver abscess cases. Rogers states (1921), that during the past ten years lesions of amœbic dysentery were found at autopsy in 77.8 per cent. of his cases of liver abscess, and scars of dysenteric lesions were found in an additional 20 per cent. However, in the majority the abscess becomes evident in the first month after the onset of the dysentery. The most common seat of the abscess is in the upper and posterior portion of the right lobe. Out of 639 cases of abscess in amœbic dysentery collected by Rouis, 70.8 per cent. were situated in the right lobe and 13.3 per cent. in the left lobe. In Charles' cases in India 85 per cent. were in the right lobe. There may be single or multiple large abscesses or very numerous small ones scattered throughout. In 562 cases Zancarol found a single abscess in 60 per cent. Waring found in 300 cases 177 solitary and 108 multiple abscesses. In Futcher's series of 18 cases, 10 were single. In the writer's series 13 were single and 10 multiple. The number of abscesses is an important factor from a surgical standpoint, the cases with multiple abscesses being more fatal.

Most authorities agree that the excessive use of alcohol by those afflicted with amœbic intestinal infection is a predisposing factor in liver abscess. Other dietetic excesses and exposure also seem to predispose to the condition. In 12 of the author's cases among private patients 8 were alcoholics. Waring found in 40 cases of abscess of the liver a history of alcoholism in 67.5 per cent. Megaw found in India that in 70 per cent. there was a history of habitual use of alcohol, and Rogers found that in 55 cases in Europeans all took alcohol, and in 16 per cent. excess was noted. Liver abscess, however, may occur in those who never partake of alcohol. In the Philippine Islands at least, malaria is generally not a predisposing factor, and Rogers states that he knows of no reliable evidence that malaria in any way predisposes to liver abscess. Kartulis reported 6 cases of liver abscess with amœbic appendicitis. In 3 the intestinal lesions were most marked in the cecum and appendix.

The amœbæ are supposed to reach the liver by two paths. The more common is certainly through the portal vein. Amœbæ are frequently found in the veins of the submucosa and in the portal capillaries and veins. The other method of transmission is through the peritoneal cavity. Councilman and Lafleur and Rogers all support this theory, and think that infection occurs in many cases in this manner. The parasites are supposed to migrate through the intestinal wall and peritoneum and then invade the liver from its surface. Lafleur cited an instance with peritonitis in which amœbæ were found over the peritoneal surface of the intestines and liver. This would certainly seem to be one mode of infection. In 1 of the writer's cases an amœbic abscess occurred beneath the right rectus muscle, the infection apparently having entered

through the parietal peritoneum. In another the abscess was less than 1 cm. in diameter, solitary and just beneath the surface of the right lobe.

Amœbæ in Liver Abscess.—In general, the amœbæ in the abscess are similar to the parasitic species (*Entamœba histolytica*) found in the intestine in dysentery. A striking fact, however, is that cysts of the parasite have not been observed either in the pus or in the walls of the abscess.

Bacteriology.—In addition to amœbæ the abscesses are often infected with bacteria. In 27 cases reported by Futcher, 15 contained bacteria; of the writer's 23 cases bacteria were found in 13, and in 37 of Rogers' they were present in 16. In the larger abscesses the bacteria may have died out, but a proportion of even the earlier abscesses seem to be entirely sterile. The organisms most frequently found are the *Staphylococcus* and the *Streptococcus pyogenes* and the colon bacillus; the *Micrococcus lanceolatus* and the *Bacillus pyocyaneus* have occasionally been reported. It is obvious why bacterial infection occurs so frequently, as these organisms have the same opportunity for entering the liver as the amœbæ and frequently adhere to them. Undoubtedly the pus cocci exert an injurious influence upon the hepatic tissue, but there can be little doubt that the amœbæ play a most important part in the formation of the abscess. This is demonstrated by the very different character of the amœbic and the pure bacterial variety. The contents of the former vary somewhat. In the small abscesses they consist of thick, glairy, yellowish masses of mucus which are not fluid. In the large abscesses the contents are more liquid, frequently like thick gruel, and yellowish, grayish-red, brownish-red, or at times greenish in portions. Microscopically one is struck usually with the absence, or presence in small numbers only, of polymorphonuclear leukocytes. The contents consist mainly of fine or coarsely granular material containing fragments of cells, many swollen and fatty degenerated liver cells, red blood corpuscles, fat globules, cholesterin crystals and amœbæ. The latter are sometimes difficult to find in the pus, but can almost invariably be obtained in scrapings made from the abscess wall, though sometimes repeated examinations are necessary to detect them.

Special Pathology.—The liver may be of normal size, but is frequently enlarged. The tissue often shows advanced fatty degeneration or chronic passive congestion or sometimes it is acutely congested. There are areas of localized peritonitis where the abscesses reach the surface of the liver, and the overlying tissues may then be bound by adhesions to it. The size of the abscesses may vary from several millimeters in diameter to that of a man's head. Very frequently several abscesses about the size of an orange are encountered. A somewhat rarer condition is that in which very numerous small abscesses are scattered throughout both lobes of the liver. The older abscesses usually have walls composed of a dense layer of fibrous connective tissue. The edge of the abscess consists of a necrotic area of liver cells where the amœbæ, together with leukocytes, blood corpuscles and fibrin filaments, are frequently found. The capillaries are dilated, filled with blood and frequently contain the parasites. The latter show no indication of attempting to penetrate beyond the necrotic zone. Outside this layer is a zone in which great

activity of the connective-tissue cells is observed and in which the liver cells are frequently compressed and atrophied; mononuclear small cells are usually abundant. Finally, this layer is usually surrounded by a zone of more marked hyperemia in which small hemorrhages are frequent. In these latter areas thrombi may occur in the branches of the portal veins, where amœbæ and bacteria may both be found. In the abscesses in which no bacteria are found microscopic examination shows that the amœbæ have apparently given rise to the necrosis and liquefaction of tissue without any very pronounced inflammatory reaction. The contents of these abscesses consist chiefly of the débris of liver tissue, with relatively slight admixture of leukocytes. In the early liver abscesses many liver cells can still be seen. There is œdema of the surrounding

Fig. 29.

Large single amœbic liver abscess.

tissue. The amœbæ are found in the edge of the living tissue and there are a few mononuclear phagocytic cells in the vicinity. Later the necrotic lining of the cavity loses its recognizable constituents and shows only a mass of nuclear fragments with a few leukocytes. The amœbæ are often found only in the margins of the living and not in the necrotic tissue, unless the abscess has been open to the air. MacCallum points out that this is because of their need of oxygen, and he emphasizes that when an amœbic abscess is first opened, frequently no amœbæ are found in the pus until the following day. After the cavity has been exposed to the air the pus may be full of active amœbæ. Councilman and Lafleur described a widespread necrosis of the cells situated around the central veins of the lobules and scattered throughout the liver. They suggested that this is due to soluble chemical products of the amœbæ.

A striking point also observed is the absence of leukocytic infiltration, which usually accompanies suppuration of bacterial origin.

Diagnosis and Symptoms.—Liver abscess is frequently overlooked, and this is not strange, for sometimes its development takes place so insidiously that perforation may be the first indication. A history of previous dysentery may suggest the condition, but an absence of such a history cannot exclude the diagnosis of liver abscess. If the onset is acute the diagnosis is simplified. Rogers[1] recognizes a *presuppurative stage* of amœbic hepatitis in which the amœbæ from dysentery lesions have lodged in the portal capillaries of the liver, but in which actual abscess formation has not taken place. In the most acute form severe *pain* appears in the hepatic region and there may be a low remittent *fever* and a *leukocytosis*, but the polymorphonuclear leukocytes are but little increased in percentage. Rapid painful enlargement of the liver sometimes occurs. At this stage Rogers believes that the disease may often be cured by emetine and liver abscess avoided. The differential diagnosis between the presuppurative and the suppurative stage is often very difficult, unless exploratory puncture is made. If chills and sweating are present and the condition is not improved by emetine, suppuration may be suspected. The more frequent indications are fever, functional disturbances, progressive enlargement and pain. *Pain* is very common at some time. It is commonly dull and aching, but may become sharp and lancinating. Its situation varies greatly, being almost as frequent in the vicinity of the right scapula and shoulder as over the liver itself. In the former case the pain is, according to Futcher, reflex through the phrenic nerve which receives large branches from the fourth cervical. The pain may occur over the hypochondrium or epigastrium. When not present spontaneously it may be elicited upon pressure over the liver. However, pain is not constant, and is frequently absent. The patient often lies on his back or on his right side, sometimes with the right leg drawn up. *Fever* is usually present at some time, but is often not sufficient to attract attention. Occasionally it is continuous and not over 100° to 102° F. In other cases it is remittent, or it may be septic in type and intermittent and rise in the evening to 104° F. Chills and sweats may then occur, and the symptoms simulate those of malaria. Lafleur calls attention to sweating as an important symptom, and states that it is independent of the temperature. The pulse may be little increased, but in the cases with high fever it may be 140 or more. There may be a spasmodic hacking cough, usually worse at night. It, however, is not peculiar in any way to liver abscess.

Blood.—The blood usually shows a moderate leukocytosis of from 12,000 to 20,000. There is sometimes a normal polymorphonuclear percentage and an increase in large mononuclears and transitional forms of from 12 to 20 per cent. The eosinophiles may be greatly reduced or absent. The leukocyte count, particularly when no bacteria are present in the abscess, may be normal. A very high polymorphonuclear leukocyte count usually occurs when infection with bacteria is also present,

[1] *International Conference on Health Problems in Tropical America*, Boston, 1924, p. 347.

while before actual suppuration has occurred the large mononuclear cells may be the variety increased. Elliot, in New Orleans, found an average of 18,000 leukocytes in 49 cases, while the polymorphonuclears averaged 79 per cent. Candler found the leukocytes in his cases to vary between 4700 and 28,000. Rogers found the counts in the great majority of his cases to be between 11,000 and 20,000.

The *conjunctivæ* are sometimes slightly tinged with yellow, but marked jaundice is rare. Persistent vomiting may occur. The skin frequently assumes a sallow color, and the face may become pale and yellow. The facies may suggest the diagnosis. In certain cases emaciation occurs rapidly; in others the flesh is well retained. The appetite usually disappears and the tongue becomes coated.

Examination may show enlargement of the liver which is usually upward and may reach as high as the angle of the scapula or cause bulging on the right side. Pain is often elicited on pressure, and particularly on sudden pressure. Occasionally a swelling is observed over the sixth and seventh ribs. Movements of the right side of the chest during respiration may be limited and the right rectus may show rigidity. If the abscess is large, percussion may reveal an increase in hepatic dulness. A friction rub may be heard over the liver when the peritoneum is involved. Crepitation at the right base of the lung with dry cough and shallow respirations may suggest the condition. The *roentgen-ray* may sometimes be an aid in diagnosis. Examination with the screen may allow of the detection of any diminution in the movements of the right side of the diaphragm, which is an important early sign, especially when the upper surface of the liver is affected. Rogers believes this sign is commonly present in the early presuppurative hepatitis, and is not an indication of actual pus formation. The right diaphragm may be nearly or quite motionless. When the liver is enlarged or an abscess is present in its upper part the right diaphragm may be raised above its normal level as well as being fixed. The spread of the inflammation to the base of the right lung may be indicated by a loss of transparency immediately above the diaphragm. While an extensive shadow in this position may indicate a secondary abscess in the lung, Rogers reports one case in which such a shadow was present without any abscess developing. He regards as of much greater importance the detection of a definite localized increase in the density of the liver shadow, for when it is well marked it may be an important sign of the presence as well as an indication of the position of a liver abscess. In the thin left lobe comparatively small collections of pus may throw a well-defined shadow. In the thick right lobe an abscess holding a pint of pus may not be shown by the roentgen-ray. The shadow is sometimes better marked in a well-localized and chronic abscess with thick fibrous walls. The roentgen-rays do not afford quite as much assistance as might be expected. Heyman[1] reported 10 cases illustrating the value of pneumoperitoneum in locating an abscess of the liver. In 8 of these cases no assistance in diagnosis was given by a roentgenograph of the hepatic area taken by the customary method,

[1] *Far Eastern Assn. Trop. Med. Trans. Fifth Biennial Congr.*, Singapore, 1923, p. 753.

but after inflation of the peritoneum with air no doubt could be entertained as to the exact position of the abscess. Occasionally the actual outline of the abscess may be discernible.

When considerable destruction of hepatic substance has taken place the *urea* excretion may be diminished. The percentage of nitrogen eliminated as ammonia may be increased in abscess of the liver. In a case reported by Rolleston crystals of leucin and tyrosin and cholesterin were present in the urine for ten weeks. On opening the abscess the urine became normal. Albuminuria is sometimes present. Pel[1] calls attention to the dysphagia in some cases which may simulate carcinoma. In the diagnosis of liver abscess there is not a single symptom that is constant, and proof that the liver is involved may be very doubtful. The general condition and appearance of the patient, with the progress of the case, rather than any single symptom, often suggest the diagnosis. An absolute diagnosis can often only be made by *aspiration* and by finding the amœbæ in the pus. A needle having a sufficiently large calibre to transmit the thick pus should be used, the puncture being made through the skin into the liver over the suspected point or points.

Spontaneous rupture of amœbic abscess frequently occurs if the patient lives long enough and is not operated upon. This is most often into the lower lobe of the right lung. Rupture into the abdominal cavity causing general peritonitis is also frequent. The abscess may perforate into the pleura, pericardium, stomach, colon, small intestine, bladder, vena cava, kidney and through the skin in the lumbar or right hypochondriac region. When the perforation occurs through the skin gangrene of the subcutaneous tissue may result.

Abscess of the Brain.—Kartulis[2] reported brain abscess as occurring in 3 per cent. of his liver abscess cases. Amœbæ were sometimes found in the vicinity of the necrotic areas. Jacob,[3] in 1911, collected 9 cases and Legrand,[4] in 1912, 45 cases from the literature, and he, Phillips, Armitage, Runyan and Herrick have recently reported 7 more cases. Europeans were most frequently affected. Twenty-seven of the cases occurred in Egypt; 5 occurred in patients who contracted dysentery in France, Germany, or England, without ever having left these countries. Runyan and Herrick's 2 cases were observed in Panama. With 4 exceptions the patients were between twenty and forty years of age; 1 case occurred in a girl, aged five years, and 1 in a boy, aged fourteen years; only 3 were in females. This complication occurs generally as an accompaniment of abscess of the liver or lung, though the symptoms due to it may not appear until the liver lesion has become quiescent or has been cured. In 2 cases at autopsy there was no apparent lesion in either the liver or lung. The abscess is usually single but may be multiple. In all but 1 of the cases it was in the cerebrum, occurring most frequently in one of the hemispheres. It may rupture into the ventricle and cause acute symptoms. In 1 case it was situated in the cerebellum.

[1] *Krankheilkunde der Leber*, Gustav Fisher, 1909, p. 140.
[2] *Centralbl. f. Bakteriol.*, 1904, **37**, 00.
[3] *Rev. d. chir.*, vol. **26**, 662.
[4] *Presse méd. d. Egypte*, 1912, **4**, 309.

Meningitis occurs only exceptionally. The contents of the brain abscesses frequently resemble those of liver abscess, being reddish in color. Necrosed portions of brain tissue attached to the wall by thrombosed vessels may be found. The microscopic appearance recalls the condition seen in abscess of the liver. In the earlier stages in which the pia mater may be affected, distended and thrombosed vessels are seen with some œdema and amœbæ in fairly large numbers. There may be leukocytic invasions of the tissue beneath the initial softening with hemorrhages. As softening takes place, a cavity is gradually formed, the contents consisting of broken-down and degenerate nerve tissue, which sometimes occurs in masses connected with the thrombosed vessels. The fluid is usually sterile bacteriologically, though both aërobic and anaërobic organisms have occasionally been isolated. The symptoms of amœbic abscess of the brain do not differ, as a rule, from those of cerebral abscess produced by bacteria. Headache is very severe, and lumbar puncture may not relieve it. The toxic evidences of suppuration are usually not prominent and there is almost no evidence of intracranial tension. The disease advances rapidly, and death usually occurs from the sixth to the eight day after onset. None of the reported cases have recovered. The patient loses consciousness and coma rapidly develops. When the abscess bursts into the ventricle the course is very acute. Convulsions may occur and the temperature may rise. In Zancarol's case the first sign was a sudden attack of mania. In others, coma may suddenly develop without preceding symptoms. Cases have been recorded in which the onset has been sudden with signs of Jacksonian epilepsy. The history of previous dysentery or the presence of amœbic cysts in the feces may suggest the diagnosis. Lumbar puncture and ophthalmoscopic and blood examinations may assist in excluding cerebral lesions due to syphilis, middle-ear disease, septic conditions, or meningitis.

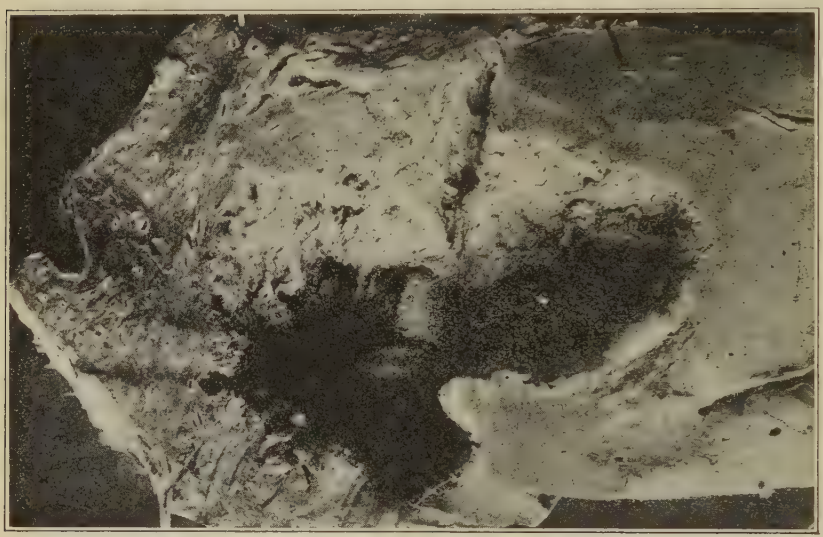
Rarer Complications.—*Abscess of the spleen* is a very rare complication. Kartulis observed but 1 case as a complication of amœbic dysentery and no amœbæ could be found in the pus. Rogers[1] has seen several cases and reported 1 in which the spleen was enlarged, and 8 ounces of thick reddish pus were withdrawn. He states that the organ is much congested and tends to become adherent to the anterior abdominal wall when fluctuation may sometimes be felt rendering aspiration easy. Under treatment by repeated aspiration and injection of emetine the mortality has been low. If opened and drained healing is liable to be slow, and a deep sinus may persist for a long time, apparently owing to the adhesions making it difficult for the organ and cavity to contract.

Jurgens reported 2 cases of *thrombosis* of the *femoral vein*, in 1 of which amputation of the leg was necessary. *Pericardial abscess* has also been observed. In 2 instances reported by Kartulis a perforation of an abscess of the left lobe of the liver through the diaphragm into the pericardial sac occurred. Sharp and Morrison (1925) have called attention to the presence of amœbæ in *multiple abscesses of the muscles* in Nigeria, in some of which they found amœbæ in otherwise sterile pus.

[1] *Bowel Diseases in the Tropics*, London, 1921, p. 382.

Abscess of the Lung.—Next to the intestine and liver, the lung is the organ most frequently invaded. The abscess may be secondary to one in the liver opening into the lung, or a primary abscess of the lung may occur independent of hepatic disease. The amœbæ may invade the lung from the hepatic veins and the abscess may result in this manner rather than by direct extension from the liver. Bunting has been able to trace emboli containing amœbæ from the thrombus in the hepatic vein which also contained parasites, and to show that this embolism of the pulmonary arteries had apparently produced the amœbic abscess of the lung. The amœbic ulcers of the intestine at the time had already healed.

Fig. 30.



Hepato-pulmonary amœbic abscess.

The formation of the abscess is usually preceded by irregular fever and an irritable cough. Preceding suppuration the respirations are usually increased in number and are often painful and shallow. Before perforation occurs the signs of pleurisy are usually present. Cough and expectoration then appear, and are generally constant. The cough in the early stages is hacking and accompanied by pain over the liver. Later the cough becomes more severe and expectoration appears. As the abscess advances definite dulness may be found with bronchial breathing or absence of respiratory sounds over the affected area. If the abscess discharges into the pleural cavity or into a bronchus the dyspnœa becomes less marked. Sooner or later the characteristic anchovy-sauce sputum appears, in which can be found amœbæ with red blood corpuscles, leukocytes, altered liver cells, alveolar epithelium, elastic-tissue fibres, Charcot-Leyden, tyrosin and hematoidin crystals and various bacteria. Small, cheesy particles consisting of granular material and oil drops are

also encountered (Fig. 30). Roentgenographic examination may be of considerable diagnostic value by revealing a dense shadow in the affected part of the lung, in addition to the fixation of the diaphragm so often seen in abscess of the liver.

Special Pathology.—In abscess of the lung the diaphragm is often adherent to the liver and usually to the base of the lung. If the latter is not the case a layer of pus may separate the lung from the diaphragm. The abscesses are not metastatic, and the lower right lobe is affected. The diaphragm may or may not be visibly perforated. On opening the lung abscess it may be found filled with viscid, yellowish-gray or yellowish-red, partially fluid material; or if perforation into a bronchus or the pleural cavity has occured it may be empty. Sections of the older abscesses show usually three zones: (1) A necrotic zone containing fragmented nuclei, degenerated cells and amœbæ; (2) a layer composed of connective-tissue cells, epithelial cells, elastic fibres, sometimes distinct groups of air cells and occasionally amœbæ; (3) a layer of small round-celled infiltration in which fibrin and some proliferation of the connective-tissue fibres are also visible between the air cells. The walls of the bronchi are thickened and infiltrated with numerous round cells. The bronchi contain purulent or serous fluid.

Abscess of the lung is a rather rare condition. It was reported by Kartulis in about 8 to 10 per cent. and by Rogers in 20 per cent. of their liver abscess cases. Harris reported it 3 times in 95 patients, and Futcher 9 times out of 119 with 3 cases in which the liver abscess ruptured into the pleural cavity. In the writer's series of 100 fatal cases hepato-pulmonary abscess occurred but once with 2 cases of empyema. When rupture into a bronchus takes place the condition may terminate in death or recovery. Before the emetine treatment was adopted the mortality was usually very high.

Peritonitis.—Local peritonitis may result from extension of the inflammatory process from the ulcerations in the intestinal wall until the peritoneal coat is invaded with deposition of lymph, fibrin and other inflammatory products on the surface of the intestine. It may also occur as the extension of an inflammatory process of an abscess of the liver. Patches of fibrous adhesions are frequent; in chronic cases it is the rule to find old localized areas of chronic adhesive peritonitis. They may cause abdominal soreness and pain. Peritonitis, which generally proves fatal, may follow perforation of a liver abscess or an intestinal ulcer.

Perforation of the intestine results generally from the giving way of the base of a deep sloughing ulcer and is most frequent in the severe and gangrenous case. The opening is usually a large one. The perforation occurs frequently in the cecum, and the condition has been mistaken for one in which the appendix is involved. Perforation of the large bowel with general peritonitis occurred in 19 of the writer's 100 autopsies on severe cases of the disease, occurring particularly in soldiers on field service. In 2 other cases it occurred after the ulcer was thoroughly walled off from the peritoneal cavity. Usually it is much rarer, occurring in about 3 to 4 per cent. of hospital cases. In Futcher's series

perforation occurred only in 3 and in Craig's in 4 cases. In the writer's series of 200 clinical cases it occurred but 3 times. In the statistical study made by Clark[1] (1925) of the cases at Panama it occurred in 10.7 per cent. of the series. In the majority the perforation occurred in the cecum, rectum, sigmoid and in 2 cases in the appendix. It is almost invariably fatal. Death may occur in a few hours from shock, or later from the resulting acute general peritonitis. Perforation sometimes happens after adhesions have formed, when a pericecal or pericolic abscess may result. It may take place retroperitoneally into the psoas muscle and may even open externally.

Appendicitis.—This complication occurred in 7 of my 100 fatal cases. In 1 a chronic appendicitis existed in connection with a pericecal amœbic abscess. In 4 of the 6, death resulted from general peritonitis following perforation of the cecum or colon. All showed extensive general intestinal lesions and the involvement of the appendix merely followed extension from the cecum. A definite diagnosis of the appendicular affection during life is very difficult, since the cecum in addition is usually extensively diseased. The process is not very acute as a rule.

Intestinal Hemorrhage.—Intestinal hemorrhage in which large amounts of pure blood are passed from the rectum is rare. In 1902 the writer called attention to severe intestinal hemorrhage as a fatal complication and reported 2 cases in both of which liver abscess was present and in which death was due to severe multiple hemorrhages. It was suggested that these large hemorrhages might perhaps bear some relation to the condition of the liver. Haasler reported from China 3 instances of intestinal hemorrhages, in 2 of which death took place from bleeding. In both of these cases liver abscess also existed. Fatal intestinal hemorrhage may take place independently of liver abscess, but when intestinal hemorrhage occurs in patients with liver abscess it is sometimes very severe and recurrent. Rogers reports 2 cases of fatal hemorrhage following operation on liver abscess.

The frequent occurrence of small amounts of blood in the stools may be explained from the fact that the walls of the veins are early infiltrated with round cells, followed by softening and complete disorganization, also from the fact that amœbæ may penetrate the walls of a vein. However, thrombosis of the veins is not infrequent.

Sequelæ.—In chronic untreated cases with extensive ulceration large cicatrices frequently form. When a long-continued catarrhal condition has been present a general atrophy of the mucosa may take place. In these instances we sometimes find a clinical condition closely resembling *sprue* or *psilosis*. The small intestine, owing to the inanition, anemia, etc., may also become secondarily involved and its mucosa atrophied. The stools then are copious, liquid (at least never formed), pale in color, and usually frothy. The chronic gastric catarrh and enteritis which frequently develop with a sore and fissured tongue and often an inflamed œsophagus complete the picture. This condition was observed in 3 very chronic patients who finally overcame the amœbic infection.

[1] *Am. Jour. Trop. Med.*, 1925, **5**, 157.

Diagnosis.—The diagnosis of amœbic dysentery can often only be made definitely through laboratory examinations, since there are other forms of dysentery which clinically it may be impossible to distinguish from it, and one who attempts to make a diagnosis from the clinical manifestations alone will make frequent mistakes. The occurrence of amœbic liver abscess always confirms the diagnosis, but sometimes the symptoms to which it gives rise are the first ones to attract attention to the intestinal disease. The examination of the stools should be made as soon as possible after they are passed, and the specimens should be collected free from urine. Many observers recommend in cold climates that a warm bed-pan be used and that the microscopic slide be gently warmed. These precautions are necessary because the amœbæ frequently die in stools that have stood for any length of time or that contain urine, and their motility is often quickly impaired by cold; motile and resting amœbæ quickly disintegrate in cold stools. Knowles, Napier and Dasgupta observed in a study of the hydrogen-ion concentration of the stools in amœbic dysentery that active motile vegetative forms of *Entamœba histolytica* were found only with a limited pH range, about 6.22. As the dysentery ceased they found *Entamœba histolytica* cysts with a pH on the alkaline side of —7.17. In recurrences of dysentery active *Entamœba histolytica* were not found in the stools when the pH was high.

In making a diagnosis the amœbæ must be found living and motile. In this condition they are more easily recognized. After movement ceases and they die it is sometimes impossible to definitely distinguish them in the unstained condition from phagocytic endothelial cells, leukocytes or squamous or mucous cells. If bloody mucus or small pieces of necrotic tissue are present these should be examined first, for if they come from the neighborhood of an ulcer they usually contain very large numbers of amœbæ. If the movements are not liquid a dose of Rochelle salts should be given and the fluid portion of the stool examined. Another convenient method of securing material for examination is by the passage of the rectal tube. When the stools are fluid considerable amounts may be obtained or small portions of mucus will be found in the lumen of the tube.

The sigmoidoscope is sometimes of assistance as it aids in obtaining material directly from the ulcers and may also reveal characteristic lesions in the intestinal wall. Some care must be exercised in using the sigmoidoscope in cases in which extensive ulceration of the rectum and sigmoid flexure exists. Cales and Froussard in a series of 200 cases recognized amœbic lesions in 25 per cent. with the aid of the sigmoidoscope, and in 12 cases they found amœbæ in the material removed from the lesions. The lesions in their cases were rarely found beyond 20 cm. from the anus.

In the latter stages of the disease or during convalescence when purgatives have been given, or sometimes after recovery from the dysentery, the cysts of the amœbæ may be found in the stools, and from their presence the diagnosis of the disease may be established. Usually, however, the cysts of *Entamœba histolytica* are not found during the most active periods of the disease, when the stools contain much mucus and

blood. In carriers who show only cysts of *Entamœba histolytica* in the stools occasionally after purging both cysts and small precystic amœbæ may be observed in the stools, and rarely the larger forms of the amœbæ containing red blood cells. Occasionally in the diarrhœal stools these small forms of amœbæ as well as the cysts may be observed.

After the presence of the motile living forms of amœbæ has been determined from the examination of the fresh specimen, the differentiation of the species of amœbæ must be made. Since it is often difficult and sometimes impossible to distinguish with certainty the species from the study of the motile vegetative forms, it is frequently necessary to examine hardened and stained specimens. In some instances when the cysts are present the diagnosis of the species can be determined more accurately. It should be borne in mind, however, that the cysts of *Entamœba histolytica* may be easily confounded by those who have not had much experience, with the cysts of other protozoa or with vegetable organisms or other cells sometimes found in the feces.

Nine different species belonging to eight different genera have been described as living in the human bowel. These are *Entamœba histolytica, Entamœba coli, Endolimax nana, Pseudolimax bütschlii, Craigia hominis, Dientamœba fragilis, Councilmania lafleuri, Karyamœba falcata* and *Caudamœba sinensis.* A description is given of each of these species with the salient features necessary for their differentiation.

Entamœba Histolytica (Entamœba Dysenteriæ, Entamœba Tetragena, Etc.)—The active amœboid parasites more commonly measure from 20 to 30 μ in diameter when they are rounded in form. The ectoplasm is hyaline, strongly developed and sharply distinguished from the endoplasm, which latter is often granular. In stools immediately after passage their movements are often active and there is explosive expulsion of the pseudopodia which are hyaline in appearance and usually contain no visible granulations. The finely granular endoplasm may contain food vacuoles and enclose red blood corpuscles or their residue or rarely a degenerating leukocyte. Some observers believe that *Entamœba histolytica* never contains bacteria or other microörganisms, but some of the apparently pathogenic entamœbæ which have been cultivated have been shown to contain bacteria in the cytoplasm. The nucleus is spherical and inconspicuous in the living forms, measuring from 4 to 8 μ in diameter. In stained specimens its chromatin is arranged in a single uniform layer of fine granules lying on the inner surface of the achromatic nuclear membrane, and often giving to the nucleus an annular appearance. There is a very small chromatin karyosome, usually surrounded by a clear area. The karyosome is typically central in position, and there is no chromatin in the area between it and the peripheral layer. Occasionally smaller so-called "precystic" forms of this amœba may be found which measure 10 to 20 μ in diameter, and which seldom contain red blood cells.

The cysts of *Entamœba histolytica* vary from 6 to about 16 μ in diameter. In some of the stools all the cysts will not be above 9 μ in diameter, while in other stools they may all measure between about 12 to 16 μ. They are spheroidal or ovoidal. At the beginning of development the

cyst contains a single nucleus which later divides into two. Each of these again divide so that the cyst when apparently mature usually contains 4 nuclei. Sometimes, however, 8 nuclei are seen and Rodenhuis observed at times as many as 12 nuclei instead of the supposedly maximum number of 4 as previously described. In developing from the uninucleate to the multinucleate stage the nuclei undergo a gradual reduction in size. In addition, the cysts usually contain a small amount of glycogen and brightly refractile bodies known as chromatoid or chromidial bodies. The glycogen is contained in a vacuole, and there may be more than one of these present in the cysts. After staining in iodine solution, Boeck gives the following characteristics for the cysts:

Cytoplasm.—Usually light brown or brown in color, finely granulated. Cysts with 1 and 2 (rarely 4) nuclei generally contain a vacuole filled with a glycogen mass with vague limits, which stains a deeper brown than the cytoplasm. Refractive chromatoidal rods, one or more in number, having rounded ends, are often present in 1- and 2-nucleated cysts less often in 4-nucleated cysts. The nuclei are 1 to 4 (rarely 8) in number. The nuclear membrane appears brownish when in focus and refractive when slightly out of focus. A minute refractive granule, the karyosome, is usually central in position. Stained with iron hematoxylin the cytoplasm is finely granulated and also appears finely vacuolated, due to fixation. Vacuoles, which previously contained glycogen, appear empty. The chromatoidal rods stain black and possess rounded ends. They are most numerous in cysts with 1 nucleus. The nuclei are 1 to 4 in number. The nuclear membrane is delicate and on it lie fine beads of peripheral chromatin. The karyosome, a small chromatin granule, is usually central in position, and faintly visible achromatic fibres radiate outward from it. A circle of minute chromatin granules may be seen about the karyosome in uninucleated cysts.

Entamœba Coli.—The motile forms measure commonly from 20 to 30 μ when rounded. The cytoplasm more commonly shows cleft-like vacuoles which often contain bacteria, yeast, starch grains and other débris. Its nucleus is somewhat richer in chromatin than the nucleus of *Entamœba histolytica*. It has a thick membrane and the peripheral chromatin is composed of large granules. The chromatic karyosome is also larger and is typically eccentric in position and not central. Adjacent to the karyosome there are often a number of smaller chromatin granules situated upon a meshwork of radiating achromatic fibres. *Endamœba coli* usually moves by a sluggish throwing out of the pseudopodia in which there is no sharp distinction visible between the ectoplasm and the endoplasm. The ectoplasm is distinctly granulated. Some authors believe that *Entamœba coli* never ingests red blood corpuscles. Lynch[1] found that an intestinal amœba which may be identified morphologically by its movements and by its cysts as *Endamœba coli*, readily ingested red blood corpuscles in the test-tube on one occasion, but failed to do so on another.

The so-called "precystic" forms of *Entamœba coli* measure usually from 15 to 20 μ in diameter. They are devoid of all food inclusions,

[1] *Am. Jour. Trop. Med.*, 1924, **4**, 43.

move sluggishly and are very similar in appearance to the corresponding forms of *Entamœba histolytica*. The nucleus, however, may be differentiated from that of *Entamœba histolytica*, as it has some characteristics as have just been described for the larger forms of *Entamœba coli*. This fact can be demonstrated in specimens stained with iron hematoxylin. The cysts of *Entamœba coli* also vary considerably in size, measuring from about 12 to 22 μ; more commonly they are from 15 to 22 μ in diameter. They are sometimes spheroidal but more usually irregularly ovoid. The cysts have slightly thicker walls than those of *Entamœba histolytica* and contain when mature 8 nuclei. They commonly contain small chromatin bodies but not large ones. Glycogen is usually present in the earlier stages, and is most abundant in the younger binucleated cysts. Cysts of *Entamœba coli* containing more than 8 nuclei are sometimes found. Some of the cysts may even contain 16 nuclei. When there are only 4 nuclei present Dobell believes that *Entamœba coli* can still be readily distinguished from *Entamœba histolytica* by the larger size of the former, and its relatively larger nuclei and more abundant glycogen. The differences in the structure of the nuclei of these two species can also be made out in the cysts. Boeck gives the following characteristics for *Entamœba coli* stained in iodine solution and in iron hematoxylin.

Cytoplasm.—This stains a deeper brown than in *Entamœba histolytica*, and is more coarsely granulated. A darker brown staining glycogen mass with vague limits is usually present in 1- and 2-nucleated cysts, but generally absent in 4- and always absent in 8-nucleated cysts. Glycogen is also diffusely present in the cytoplasm. The chromatoidal rods rarely occur, but when present they appear as refractive splinter-shaped or ribbon-like bodies in 1- and 2- or 4-nucleated cysts. The nuclei are 1 to 8 in number. The nuclear membrane appears dark brown when in focus and refractive when seen slightly out of focus. Nuclear membrane is thicker than that of *Entamœba histolytica*, and on it lie larger refractive chromatin granules, easily observed with the oil-immersion lens, in 1-, 2- and sometimes 4-nucleated cysts. The karyosome is generally eccentric in position and is large compared to the minute central karyosome of *Entamœba histolytica*. Occasionally 2 karyosomes are visible as in 1 of the nuclei. In iron hematoxylin the cytoplasm is coarsely granulated and vacuolated. Vacuoles, which previously contained glycogen and now appear empty, are usually present in 1-, 2- and 4-nucleated cysts. Chromatoidal rods when present stain black, and are splinter-shaped or more rarely as ribbons. The nuclei are 1 to 8 in number. The nuclear membrane is thicker than that in *Entamœba histolytica*. The peripheral chromatin lies in large blobs on the nuclear membrane and a few granules lie in the area between it and the karyosome. The karyosome differs from that in *Entamœba histolytica* in that it is a larger chromatin granule and lies eccentric in position. Faint achromatic fibres radiate outward from the karyosome. Occasionally cysts are seen in which the nuclei are dividing and appear spindle-shaped instead of circular.

Endolimax Nana (Vahlkampfia Nana).—The free-living amœbæ of this species are very small, with a diameter of 5 to 10 μ. They may be

vacuolated and contain bacteria and cocci, or appear quite homogeneous. This amœba, as a rule, moves sluggishly, throwing out one or more blunt pseudopodia. It does not glide along in the true *limax* manner. The nucleus with its large chromatin block can sometimes, though rarely be detected in the living amœba. In stained preparations the amœbæ show the same clear or vacuolated cytoplasm seen in life. The structure of the nucleus can, however, be more clearly seen. Generally this appears to be of the karyosome type with a clear nuclear membrane and a large, centrally arranged chromatin block or karyosome which is often irregularly shaped. The position of the chromatin block at the centre of the nucleus is often only apparent, for in certain positions of the nucleus it is seen to be lying laterally against the nuclear membrane. In those cases in which it seems to be centrally situated the appearance may be due to the nucleus lying with the chromatin mass on the upper or lower surface of the nuclear membrane, as the amœba lies on the slide. Sometimes the laterally placed chromatin mass is connected with a filament which passes across the nucleus to a granule lying on the nuclear membrane opposite to it. The occurrence of this type of nucleus is important, for it is a very common type in the encysted forms, and may assist in the determination of the species of the cyst.

The *cysts* of *Endolimax nana* are oval, spherical, or more irregularly shaped structures, having a diameter of 7 to 8 μ when spherical, and a length of 8 to 10 μ when elongated. The latter type is most easily recognized as a pale, whitish and structureless body, in which no detail can be detected. Even when mounted in iodine it is only occasionally that the external nuclei can be seen. The cysts of this amœba have hitherto been regarded as structures of vegetable nature. Fixed in Schaudinn's fluid and stained with iron hematoxylin solution, the nuclear details can be as clearly seen as the small size of the cysts permit. There are either 1, 2 or 4 nuclei, and these are generally grouped toward the end of the cyst. When mature the cyst contains 4 nuclei. The structure of the nucleus in the cyst corresponds to that in the free amœbæ. They contain no chromatoid bodies, but usually a few bright granules. This species is regarded as non-pathogenic, but it is of importance on account of the possibility of its being confused with *Entamœba histolytica*. However, the structure of the nucleus when stained is diagnostic.

Pseudolimax Bütschlii (Iodamœba Bütschlii).—The amœbæ of this species when motile resemble small specimens of *Entamœba coli* or large ones of *Entamœba nana*. They measure from 9 to 20 μ in diameter, but more commonly are from 8 to 12 μ. The organisms quickly die and disintegrate in the stools. Their movements are usually feeble. The ectoplasm is not conspicuously differentiated from the endoplasm, and the latter contains numerous vacuoles enclosing bacteria. Dobell points out that the most distinctive feature is the nucleus. It is vesicular with a delicate membrane, and contains a fairly large and homogeneous central karyosome consisting of chromatin. Between the karyosome and the nuclear membrane there is always a zone occupied by a layer of fine granules which stain feebly with chromatin stains, but readily with plasma stains such as eosin.

The cysts, formerly known as iodine cysts, are uninucleate and usually measure from about 9 to 12 μ in diameter. They are commonly irregular in shape and may be ovoid, spheroidal, triangular, square or fusiform. The nucleus of the cysts differs from that of the free form in having its karyosome peripherally placed and in possessing more abundant granules. The cyst usually contains a large and sharply-defined mass of glycogen which stains deep brown with iodine. Sometimes more than one glycogen mass is present, but rarely this mass is absent. In stained preparations the area occupied by the glycogen is represented by a sharply-defined vacuole. In addition the cysts usually contain a number of very brightly refractile granules which Dobell states are probably composed of volutin, not chromatin.

Craigia Hominis (Paramœba Hominis).—This amœba was described by Craig as a small, free-living or parasitic amœba, with a uniflagellate swarmer stage. In the amœba stage they measure from 10 to 25 μ in diameter with little differentiation into ectoplasm and endoplasm when quiet, but with anterior ectoplasm in movement. The endoplasm is granular and contains a nucleus which is composed almost entirely of chromatin. The endoplasm is with or without an extra nuclear body. The cysts of the organism have been observed. After development within the cyst the wall ruptures and the spores escape as uniflagellate swarm spores constituting the flagellated stage. Later the flagellates cease to move, lose the single flagellum and become amœboid in character. Craig and Barlow described this organism as probably producing chronic diarrhœa and dysentery in man. Many authors believe that this amœba should be classified with the flagellates.

Dientamœba Fragilis.—This amœba, first described by Jepps and Dobell, as a small and rare amœba, is distinct from all the others by being typically binucleate. According to these authors it usually measures from about 5 to 11 μ in diameter. Its movements are snail-like, and it is extremely delicate, soon dying outside the body. The organism feeds upon bacteria which are usually present in vacuoles in its endoplasm. The two nuclei are identical in structure, each consisting of a minute vesicle about 1.5 to 2 μ in diameter, with a central karyosome composed of a number of chromatin granules. A clear zone containing no granules lies between the karyosome and the nuclear membrane. In addition to the binucleate forms uninucleate individuals also occur, their nuclei being structurally identical. The cysts of this species are unknown. Taliaferro and Becker[1] (1924) have tabulated thirty-three infections in all with this amœba. They conclude that this small number of cases is probably due both to the fact that the amœboid form degenerates so quickly after leaving the body, and that the cysts are unknown.

Councilmania Lafleuri.—Kofoid and Swezy give the following characteristics. Free stage with hyaline pseudopodia, abruptly formed, endoplasm filled with food vacuoles and even ingested red blood corpuscles, resting nucleus with moderately thin zone of peripheral chromatin, karyosome generally eccentric, often with small halo, in premitotic

[1] *Am. Jour. Hyg.*, 1924, **4**, 71.

stages composed of dispersed particles and more nearly central in location. Pseudopodia broad, rounded, usually less than diameter of the body in width, generally single. Cysts with 1, 2, 4 or 8 nuclei, rarely more, thick walled, triple contoured, spheroidal, ellipsoidal or asymmetrical, less frequently spherical. Nuclei of cysts with little peripheral chromatin and large, eccentric or central, spheroidal, reniform, or lobed karyosome often divided into scattered particles, 8 chromosomes and an intradesmose joining polar masses seen best in first and second mitoses. The cysts form a chromophile ridge from which cytoplasm emerges through a pore in the cyst wall as a chromophile bud. A nucleus migrates into the bud which detaches as an amœbula. The process is repeated until the cyst is emptied of nuclei. Budding may occur in the bowel. Free stages from 63 to 35 μ to 20 to 35 μ when rounded up; spheroidal cysts 16 to 20 μ, rarely 8 to 34 μ in diameter. Parasitic in the human intestine. Type species, *Councilmania lafleuri.*

Karyamœba Falcata.—Three instances of infection of man of this amœba have been reported in 1924 by Kofoid and Swezy. All 3 were accompanied by infection with *Endamœba dysenteriæ,* but the former amœba persisted after treatment for amœbiasis, and with no clinical signs of pathogenicity. It occurs in the motile phase only. Mitosis and binucleate amœbæ and rounded (precystic) phases were found. This amœba is characterized by 1, rarely 2 or more, blunt, hyaline pseudopodia. Ectoplasm and endoplasm are sharply separated. There is a heavy peripheral pellicle, a narrow, clear, ectoplasmic zone beneath it, and an inner ectoplasmic mass of greater or lesser volume sharply set off from the more granular endoplasm. The endoplasm is coarsely vacuolated; food bodies are rare in these vacuoles. The nucleus contains one or two, rarely more, large, crescentic, siderophile masses, applied to the nuclear membrane and little peripheral chromatin otherwise applied to the membrane. There is a neatly spherical, eccentric karyosome in a halo adjacent to which a minute centriole is sometimes found. There is no concentric zoning of the intermediate region. Mitosis proceeds by the emergence of polar caps, apparently from the crescentic masses, the division of the centriole and the migration of the daughters to the poles over the outside of the polar cap on whose summit the centriole lies in the centre of a lighter halo. The centrioles are joined by a slender, thread-like, meridional intradesmose. Chromosomes emerge probably from peripheral chromatin as elongated masses in the area between the polar caps. These shorten up into two rows in an end-to-end arrangement in the amphiaster stage. There are approximately 20 chromosomes. Mitosis is of the *Vahlkampfia* type. It differs from *Vahlkampfia* in the small size and eccentric location of the karyosome and in the abundance and crescentic massing of the peripheral chromatin.

Caudamœba Sinensis.—This is reported as occurring in North China by Faust in 4 cases. It is regarded by him as pathogenic and capable of producing amœbic dysentery. In all 4 cases the organism contained red blood cells. The patients were cured by treatment with emetine. Faust describes this amœba as follows: When not quiescent it measures 16 to 17 μ in diameter. The organism is characterized by viscous endo-

plasm, thin layer of ectoplasm, antero-posterior polarity, lobose anterior and attenuate posterior end drawn out into a caudostyle, which is surrounded at times by a group of protoplasmic projections more or less conspicuous, a constant movement of the organism away from the caudal end, and a nucleus near the anterior end of the body with minute chromatin granules just within the nuclear membrane which in stained fixed specimens are seen to be connected with achromatic fibrils. The karyosome is specifically different from that of the described entamœba of man, consisting of a star-shaped clump of chromatin with a hollow centre in the centre of the nucleus with radiating lines of chromatic granules.

Stained specimens are often necessary before the diagnosis of the species can be made. The character of the nucleus and the distribution of chromatin in the nuclei is frequently of assistance in differentiation. When the cysts are present their examination in stained preparations usually gives even more accurate means of differentiation of the different species. For stained preparations either Schaudinn's well-known alcohol sublimate, iron, hematoxylin method, or Donaldson's iodine-eosin staining method as modified by Kofoid, Kornhauser and Swezy, gives the most satisfactory results.

Castellani calls attention to the further differentiation of the cysts. First, cysts of the amœbæ of the *limax* type are found in older stools, are always small, uninucleated and often have a thick wall of brownish color. The cysts of *Chilomastix mesnili* are usually lemon-shaped, possessing an elevation of the cyst wall, slightly thickened at one end. These cysts are also characterized by the presence of the parabasal deeply staining chromatic fibre. The cysts of *Giardia intestinalis* are recognized by their egg-shaped appearance; they are about 14 μ in length and very transparent, so that the lamblia can be seen within it with the characteristic central paired rod-like structure in which originate the four pairs of flagella. The cysts of *Oicomonas, Bodo, Prowazekia* are very small, spherical, 6 to 8 μ in diameter, uninucleated, very similar to those of *Amœba limax,* but the wall is not so thick nor of brownish color, and the outline is more regular. Sometimes it is impossible to distinguish these cysts from those of *Amœba limax.* They can always be differentiated from those of *Entamœba histolytica,* as they are very small and uninucleated. *Blastocystis hominis* may be sometimes confused with the smaller protozoan cysts. Its cysts are more or less spherical and 5 to 15 μ in diameter, with a more delicate capsule than the cysts of *Entamœbæ.* They contain usually a very large vacuole, which reduces the cytoplasm to a narrow rim at one pole or both poles of the cyst. After staining in iodine solution this thin rim is seen to be finely granulated and vacuolated.

Of the nine species of amœbæ described in man, *Entamœba histolytica, Councilmania lafleuri* and *Caudamœba sinensis* have all been observed to ingest red blood corpuscles and are supposed to be pathogenic while the other species have been regarded as non-pathogenic for man. However, only in the case of *Endamœba histolytica* and *Entamœba coli* have satisfactory experiments been performed upon animals with relation to

pathogenicity. Regarding the remaining species, it can only be said that they have been observed in individuals with no symptoms of intestinal disease. Obviously, even the protozoölogist will find the differentiation of amœbæ difficult at times. Indeed, sometimes we are not able to say with certainty whether a motile amœba in the stools is pathogenic or non-pathogenic for man under certain conditions. Sometimes the clinician, from his observation of the symptoms of the patient over a long period of time, is more capable of answering this question than the laboratory worker from the microscopic examination of the amœba alone. A few observers incline to the belief that all motile amœbæ found in the intestine may be or may become pathogenic for man. We know nothing as to whether the pathogenesis of some species of amœbæ under certain conditions may be increased and the whole subject of the classification and diagnosis of the species of pathogenic and non-pathogenic amœbæ is still in a very unsatisfactory state. While the differentiation of species of amœbæ in the human intestine has become of great interest to the specialist, it has not been of exceedingly great benefit to the clinician. This is particularly so because, while there are very few specialists who are sufficiently familiar with the morphological details to distinguish the various different species of motile amœbæ which have been described in the intestine of man, only plausible guesses may sometimes be made with reference to the clinical significance of the parasite, unless the condition of the stool is taken into account and the presence or absence of blood, mucus, intestinal epithelium, leukocytes, or other cells, and Charcot-Leyden crystals are taken into consideration.

If the clinician finds motile amœbæ in stools which also contain blood and mucus, and particularly if the amœbæ contain red blood corpuscles, he is justified in a diagnosis of amœbic enteritis and in instituting treatment against the parasite. If, on the other hand, the patient has never had any intestinal disturbance or symptoms, and a fresh stool appears normal in every way with the exception of the presence of a few amœbæ which answer to the description of *Entamœba coli* or other non-pathogenic types, it would seem advisable that the patient be kept under close observation with occasional examination of the stools and an expectant plan of treatment. In some patients with chronic relapsing amœbiasis it may be extremely difficult to find amœbæ after the most prolonged and careful search.

Differentiation by Immune Reactions.—Sellards showed that biological distinctions may be demonstrated in amœbæ by the employment of specific sera. Izar obtained positive complement-fixation reactions with serum from 5 human cases of amœbic dysentery and with serum from 3 cats experimentally infected from man. He used in these tests aqueous antigens prepared from the feces of infected cats, or the pus from the liver abscess of man. Normal feces or feces from cases of bacillary dysentery used as controls reacted negatively, nor did the normal sera of man or cat react with either antigen. Hager was unable to confirm Izar's results. Schuckmann differentiated by specific agglutinins several different strains of saprophytic amœbæ, and complement deviation reac-

tion was also obtained. Wagener[1] (1924) found that after infecting cats with *Entamœba histolytica*, those animals infected for a week or longer, after amœbæ were observed in the stools, gave a positive precipitin test with an antigen prepared from scrapings of the ulcerated areas in the intestine. The serum from normal cats or from cats infected for less than a week gave only negative precipitin tests. In preparing the antigen the scrapings from the ulcers were put immediately into Coca's extracting fluid composed of 0.5 per cent. sodium chloride, 0.05 per cent. bicarbonate of soda and 0.4 per cent. phenol. This fluid was then covered with toluol. The scrapings were allowed to autolyze for several days, preferably a week, and the material was then filtered through hard filter paper, sterile filter paper and glassware being used.

Scalas[2] employed the *intradermal reaction* in amœbic dysentery for diagnosis. The antigen used for this test was prepared as follows: 30 gm. of mucus and small fragments of intestinal mucosa from the fresh feces of a case of acute amœbic dysentery were treated with 30 c.c. of normal saline in a stoppered vessel containing glass beads and placed in a thermostat at 37° C. for a week with daily shaking. The product is then filtered, first through a paper and afterward through a Berkefeld filter connected with an exhaust pump. The filtrate is decolorized with animal charcoal and sterilized. For the test 0.25 c.c. is injected intracutaneously. A positive result is shown by a swelling on a large red base, 5 to 6 cm. in diameter, appearing in an hour with itching and a sense of heat but no actual pain. The signs fade in one to three days. In negative cases there is merely an erythema with no œdema, local heat or discomfort. In 9 cases of amœbic dysentery the test proved positive, while in 23 others, either healthy or suffering with other diseases, the test was negative. Thus far serological tests have not become of practical importance in diagnosis, but when improvement in the technique of cultivating the *Entamœbæ* is made these reactions may assume greater significance.

Roentgen-ray Examination.—Roentgen-ray examination after administration of bismuth or barium by the mouth or by enemata has been advocated as of assistance in diagnosis, and particularly in determining the severity of the invasion and extent of the defects in the intestinal wall. Vallarino[3] believes that through its employment he was able to determine the extent of the intestinal lesions and to give the clinicians data which they could not obtain by any other means. He noted that the defect found in the majority of the cases was a mottling of the affected part. The bowel loses its normal contour and a mottled area is found, the extent of which depends on the degree of the intestinal lesion. This is explained on the belief that the mucosa of the intestine in this region is ulcerated and inflamed, and leaves only a small and irregular part of the lumen of the intestine into which the opaque substance can enter in various densities which result in the defect found in the lumen. At other times, and particularly in old cases, defects resembling obstructions are found which may be attributed to isolated patches of infected

[1] *Univ. California Pub. Zoöl.*, 1924, **26**, 15.
[2] *La Riforma medica*, 1923, **39**, 967.
[3] *Am. Jour. Trop. Med.*, 1925, **5**, 149.

intestine. He obtained better results by giving the opaque substance by the mouth than by administering a barium enema. While the clinical symptoms usually conformed to the roentgen-ray findings, sometimes a more extensive ulceration was indicated by the films than the clinical symptoms led the clinician to suspect. In the vast majority of cases, however, the diagnosis can be made without the aid of the roentgen-ray.

Differential Diagnosis.—Bacillary dysentery is the most important disease with which amœbic dysentery may be confused. Stitt points out that it is possible as a rule to differentiate bacillary from amœbic dysentery by the more sudden and acute onset of the former, together with fever and other evidences of toxemia. The pulse-rate is more rapid in bacillary than in amœbic dysentery, and the number of stools is usually greater, although the amount of each stool is less in quantity. He also believes that the character of the stools in the two affections may aid in diagnosis. Manson-Bahr enumerates the points on page 280 of differentiation between amœbic and bacillary dysentery.

Charcot-Leyden crystals have been found in from 20 to 25 per cent. of amœbic dysentery cases, and Thomson considers their presence to be diagnostic of amœbic dysentery as opposed to bacillary disease. Wilmore and Shearman, Wenyon and O'Connor, Manson-Bahr, Graham, Anderson and Haughwout[1] have laid great stress upon the diagnosis of bacillary dysentery from the microscopic examination of the stool and from the typical cell picture so often observed. Great stress is laid on: (1) The presence of polymorphonuclear cells to the extent of about 90 per cent. of the total cellular exudate; (2) the presence in varying proportions, about 2 to 10 per cent., of endothelial macrophage cells varying from 15 to 20 μ in diameter, many of which have phagocytized erythrocytes; (3) evidence in the various cells composing the exudate of an extreme necrotic process which results in a uniform and simultaneous destruction extending to all parts of the cell. In extreme cases only the cell membrane and a slight residuum of former protoplasmic substance remain, such constituting the so-called "ghost" cells which with the macrophages are said to be diagnostic of bacillary dysentery. Cells of other types, such as epithelial cells, plasma cells and leukocytes of various kinds, occur in small proportions in bacillary dysentery. In *amœbic disease* the exudate is said to be mostly mononuclear in character with proteolytic digestion of the protoplasm, but well stained and preserved nuclei. In bacillary disease in the early acute stage numerous columnar epithelial cells derived from the surface of the mucous membrane are more frequently seen than in amœbic disease. However, the above characteristics are of more importance in the early recognition of bacillary dysentery than in the exclusion of amœbic dysentery. For the accurate differentiation of the two affections either the amœbæ must be demonstrated or *Bacillus dysenteriæ* isolated from the stools. Mixed infections with both amœbæ and *Bacillus dysenteriæ* sometimes occur. Fletcher and Jepps,[2] in a study of 198 cases of amœbic dysentery in Singapore, isolated *Bacillus dysenteriæ* from 27 of the cases.

[1] *Philippine Jour. Sci.*, 1924, **25**, 513.

[2] *Dysentery in the Federated Malay States, No.* 19 *of Studies from the Institute for Med. Res., Kuala Lampur*, London, 1924, p. 73.

Bacillary Dysentery.	Amœbiasis.
An acute disease with a tendency to epidemic spread.	A chronic endemic disease.
Incubation period a short one, seven days or less.	Incubation period a long one, at least twenty to ninety days; it may be more.
Onset acute.	Onset insidious.
Pyrexia common.	Pyrexia rare, unless complicated.
Course, days or weeks.	Course usually prolonged.
Complications: No hepatic symptoms; polyarthritis frequent.	*Complications:* Hepatitis, abscess of liver, more rarely in other situations.
Death due to: (*a*) Exhaustion and (*b*) toxemia.	Death due to: (*a*) Exhaustion, (*b*) perforation, (*c*) hemorrhage and (*d*) liver abscess.
Signs: General tenderness over whole abdomen; more marked over sigmoid flexure.	*Signs:* Local tenderness and thickening, mostly over sigmoid flexure, transverse colon and cecum.
Tenesmus very severe.	Tenesmus not accentuated.
Ulcers: When present, on free edge of transverse folds of mucous membrane and distributed transversely to long axis of gut; serpiginous in their outline, with ragged undermined edges, often communicating with neighboring ulcers; bases consist of granulation tissue; intervening mucous membrane hyperemic; rarely perforate; no compensatory thickening of bowel wall.	*Ulcers:* Commence as small abscesses of submucosa, distributed in long axis of gut; oval in shape, regular in outline; flask-shape in section, involving all coats; bases consist of necrotic black tenacious sloughs; not uncommonly perforate; compensatory thickening of bowel wall; intervening mucous membrane not affected.
Stools: Scanty; many in number; bright blood-red, gelatinous, viscid mucus, odorless, resembling red-currant jelly.	*Stools:* Feces intermingled with blood and mucus, resembling anchovy sauce; very offensive, smelling of decomposing blood; generally copious.
Microscopic picture: Numerous red cells; polymorphonuclears numerous, with clear-cut ring nuclei; macrophage cells may be numerous; few visible microörganisms.	*Microscopic picture:* Red cells numerous and in clumps; polymorphonuclear cells much damaged, often extruded nuclei; macrophage cells scarce; large numbers of motile bacilli, *Entamœba histolytica*, generally with ingested red cells; Charcot-Leyden crystals common.

Amœbic dysentery must also be differentiated from the other forms of intestinal flux, such as balantidial, schistosomal and malarial dysentery. These diseases, however, can be at once differentiated by the

finding of the characteristic parasites from a microscopic examination of the stools or blood. Tuberculosis of the intestine sometimes may be confused. The tubercle bacilli can in some cases be detected in the feces. Examination of the lungs and sputum obviously may be of assistance if tuberculosis is present.

The *diagnosis of liver abscess* should be made only after a careful consideration of all existing symptoms. The general condition of the patients and his feces together with the progress should be taken into account. The blood should be examined to exclude malaria and for a leukocytosis, but the leukocyte count may occasionally be almost normal. Rogers[1] believes that a presuppurative stage may be recognized when a marked leukocytosis is present and there is little or no increase in the proportion of polymorphonuclear leukocytes. The roentgen-ray findings have been mentioned. The possibility of echinococcus cyst or gumma should be considered. If no intestinal disturbance exists a clue may be obtained from the history or by finding the amœbæ in the stools. An absolute diagnosis can frequently only be made by the finding of amœbæ in the abscess. This may sometimes be done by aspiration. A needle having a sufficiently large calibre to transmit the thick pus should be used. The puncture may be made through the skin, the point of entrance being over the suspected area; but the surgeon must be at hand to operate if necessary. When pus is obtained it may contain no amœbæ, but the absence of large numbers of polymorphonuclear leukocytes and the presence of much granular material will suggest that the origin is amœbic.

The diagnosis of amœbic hepato-pulmonary abscess may be definitely made when the patient suddenly begins to expectorate quantities of reddish-brown anchovy-sauce sputum containing liver cells, hematoidin crystals and amœbæ. The latter are almost invariably present, though sometimes a prolonged search is necessary to find them.

Prognosis.—In the tropics, and particularly in temperate climates, one sees fewer of the more severe and more advanced cases of amœbic dysentery than formerly, and fewer serious complications. In many cases, formerly considered hopeless before emetine was employed, the patients frequently recover. In untreated patients who are exposed to hardships and away from hospital facilities and physicians, the death-rate may be as high as 30 to 40 per cent., while in cases treated properly with emetine the mortality should not be over 10 to 12 per cent. Rogers had in earlier years a mortality of 43.3 per cent. in cases treated with ipecac, but after the introduction of the treatment with hypodermic injections of emetine the mortality was reduced to about one-fourth of what it was formerly.

Hiccough, seen particularly in the severer forms, often indicating involvement of the peritoneum and the approach of exhaustion and death, is a very unfavorable sign.

In the uncomplicated cases, those with acute onset, including the gangrenous form, usually have the gravest outlook. Cases with a mild onset when treatment is instituted early are usually cured promptly.

[1] *Practitioner*, June, 1907, p. 776; also *Fevers in the Tropics*.

In children the prognosis is almost always good. Of 44 collected cases, even before the introduction of emetine, there were but 2 deaths.

Spontaneous rupture of liver abscess frequently occurs if the patient is not operated upon. In those cases in which the abscess ruptures into the lung the prognosis is fairly favorable. Rupture into the peritoneal cavity and pericardium is practically always fatal. While rupture into the lower lobe of the right lung is most common. Cyr's statistics of 159 cases show that rupture occurred into the lung in 59, into the pleural cavity in 31, into the peritoneal cavity in 39, into the intestine in 8, into the stomach in 8, into the vena cava in 31, into the kidneys in 2, into the bile ducts in 4, into the pericardium in 1 and externally in 2. Attention has been called to a number of cases in which cutaneous abscesses developed in the skin and in the gangrenous subcutaneous tissue in cases of liver abscess. Sambuc found that where only one liver abscess was present the mortality was 23 per cent.; with two abscesses, 45 per cent.; with three abscesses, 90 per cent.; with more than three abscesses, 100 per cent. In Roger's European cases it occurred in 20 per cent. When rupture into a bronchus takes place the abscess may discharge for months, or the disease may end fatally in a shorter time. In favorable cases the pus diminishes and the cavity cicatrizes, but complete recovery may be delayed for over a year. Hodson reported 2 cases of liver abscess which had ruptured through the lung in which the patients recovered at once after treatment with emetine.

While the prognosis is still often grave in liver abscess the outlook has been greatly improved since the employment of emetine. Before its use the mortality in the tropics was usually over 50 per cent., and even under careful surgical treatment usually not more than one-third recovered. Thus in the Johns Hopkins Hospital Futcher reported 19 deaths out of 27 cases; 17 of these were operated upon but only 5 recovered.

Immunity.—While in many instances there seems to be a natural resistance to the disease, it would appear doubtful if there is any acquired immunity against it. The apparent natural resistance may depend upon the fact that the parasites are killed before reaching the large intestine, or that they do not find favorable conditions for further propagation. The amœbæ, after the development of the disease, may disappear from the stools independently of treatment, but this may be brought about by unfavorable conditions in the intestine rather than by any acquired immunity.

Treatment.—Emetine is perhaps almost as specific in the treatment of amœbic dysentery as is quinine in malaria. Emetine is an alkaloid of ipecac which is contained in the dried root of a Brazilian herb, *Psychotria* or *Cephælis ipecacuanha*. This plant was said to have been in common use in parts of South America long before it was brought to Europe by Piso, about 1650. The late Sir Patrick Manson for many years advised its employment in all forms of dysentery. Partially, no doubt, on account of the emesis which the drug generally produces when given by mouth, it never became popular. In 1817 Pelletier isolated an alkaloid from ipecac which he named "emetine." It was later shown that this substance was in reality a mixture of three alkaloids. In 1894 Paul

and Crownley demonstrated that the root contained a second alkaloid to which the term "cephælin" was given. Still later a third alkaloid, psychotrin, was isolated, and Pyman demonstrated that this alkaloid on reduction gives rise to cephælin and isocephælin. Another substance, the methyl ether of psychotrin, was shown to give rise to emetine and isoemetine. Walters and Koch experimented particularly with synthetic derivatives of cephælin and have found that cephælin-iso-amyl-ether-hydro-iodide was effective in destroying both the vegetative and the encysted amœbæ in the intestinal tract of cats. Psychotrin and methyl-psychotrin, which are comparatively non-toxic, are said by Dale, Dobell, Jepps and Meakins to be therapeutically inactive in amœbic dysentery. A preparation known as "ipecacuanha sine emetina," which produces no emesis, has also little favorable effect in the treatment of the disease.

The two most important alkaloids of ipecac in the treatment of amœbic infections are *emetine* and *cephælin*. Emetine is slightly soluble in water, readily soluble in alcohol, ether, chloroform and benzene. The two salts recommended for medical use are the hydrochloride and the hydrobromide. The hydrochloride has a greater solubility than the hydrobromide and is more applicable for general use. When given in toxic doses this alkaloid depresses and may eventually paralyze the heart. It causes a definite derangement of metabolism, and is a powerful gastrointestinal irritant when given by the mouth. When given subcutaneously in small doses the drug does not usually exert its emetic and expectorant properties. Cephælin, which is more toxic than emetine, is less soluble in ether, but readily soluble in caustic alkali solutions. While it has similar medical properties to emetine, it is a more powerful emetic and its subcutaneous administration is said to produce greater irritation and pain at the site of puncture than emetine. Since emetine is less toxic than cephælin it has generally been employed in the treatment of amœbic dysentery. The best results have been obtained with it, but it does not always bring about the destruction of all the amœbæ or cause amœbic ulcerations to heal immediately. Its curative action is often proportional to its early employment in the acute attack. In cases with advanced lesions where there is much destruction of tissue, and where secondary infection of the lesions with intestinal bacteria has occurred, its effects are not so noticeable. Doses of $\frac{1}{2}$ gr. (0.032 gm.) twice daily, or $\frac{1}{3}$ gr. (0.02 gm.) three times daily of emetine hydrochloride dissolved in sterile saline solution, may be administered by hypodermic injection into the subcutaneous tissues for a week to ten days at a time. Children aged eight years may be given $\frac{1}{3}$ gr. daily and younger children $\frac{1}{6}$ gr (0.01 gm.) daily. Some recommend higher doses, but amounts of 0.3 to 0.4 gm. have produced very serious symptoms, such as dyspnœa, vascular paralysis, vomiting, thin stools and marked slowing of the pulse. A dose of 1 gr. (0.065 gm.) daily is usually within the margin of safety. Unless patients are treated for a week or ten days with emetine, relapses are liable to occur. Vaccarezza believes that he obtained better results using a maximum dosage of $2\frac{1}{3}$ gr. (0.15 gm.) daily for not more than four days, or $1\frac{1}{2}$ gr. (0.1 gm.) for not more than seven days. Some pain may be caused by the emetine injections. Cawston states that this can

be avoided by dissolving the alkaloid in 1 per cent. phenol immediately before injection into the *muscles*. Petzetakis[1] recommended intravenous injections. He gives gradually increasing doses, commencing with 0.03 gm. up to a maximum of 0.1 gm. ($1\frac{1}{2}$ gr.), making a total of 0.35 to 0.45 gm. (7 gr.) within ten days. From these injections he reports rapid and striking results superior to the intramuscular or subcutaneous methods. However, he reports a fatal case after a single injection of 0.35 gm. Intravenous injection of the drug is obviously more dangerous and is not recommended by the writer.

The physician should bear in mind that emetine is poisonous and that there may be cumulative action of the drug which may manifest itself in asthenia, polyneuritis and cardiac complications. In patients who do not yield to treatment in a week or ten days the drug should be interrupted for a short period before a second course of treatment is instituted. Kilgore has noted several cases of peripheral neuritis after treatment with emetine, which usually manifested itself in general muscular pains and weakness, especially in the legs, progressing sometimes to paresis. Wrist-drop and toe-drop were common. The symptoms disappear gradually on stopping the emetine. Severe neuritis was produced in 1 case from a dose of 19 gr. and in a second case from a dose of 6 gr. Levy and Rowntree collected from the literature 20 cases of poisoning from the use of emetine. In 6 of these less than 10 gr. were given. All recovered except 1 case in a man who received daily subcutaneous injections of $1\frac{1}{2}$ gr. of emetine hydrochloride for twenty days, a total of 29 gr. Diarrhœa seems to be an important symptom of emetine poisoning and the diarrhœa produced by large or prolonged doses of emetine may be confused with that due to the dysenteric process. Rogers believes that 15 gr. of emetine usually constitutes a fatal dose for an adult man.

Many cases of amœbic dysentery, particularly those with advanced lesions, do not yield to treatment with emetine, and relapses after the use of the drug are not very uncommon. It is especially active in destroying the vegetative forms of the amœbæ which are being passed in the stools, but is often not so effective in ridding the patient who is passing cysts of the infection. While the hypodermic administration of the drug in moderate doses generally causes no nausea or vomiting, some observers believe that it is less effective than when given orally. Wenyon and O'Connor recommend a combined subcutaneous and oral administration of the drug. One grain of emetine is given by injection in the morning and $\frac{1}{2}$ gr. of emetine in tablet form at night. This treatment has been used especially in the subacute and chronic cases.

A number of pharmacological preparations have been made with the object of reducing the nauseating and emetic effects of emetine, and at the same time retaining its therapeutic action, but these have not been found satisfactory. Some observers believe that it is more advisable to employ ipecac rather than its alkaloid emetine, and Manson-Bahr has pointed out that the value of ipecacuanha in certain instances is still

[1] *Presse méd.*, 1924, **32**, 705.

undoubted. Salol-coated ipecac pills have been particularly advocated in the United States with the object of avoiding the nausea and vomiting. Stitt reported success by the administration of ipecac by the duodenal tube. Alcresta is apparently an absorption compound of the ipecac alkaloids of emetine alone with hydrated aluminum salicylate. While it is less likely to cause vomiting, probably on account of the insolubility of the alkaloids in this form, the results in treatment with it are said to have been far less satisfactory than those obtained with emetine.

Emetine Bismuth Iodide and Emetine Periodide.—For cases of amœbic dysentery which do not yield to emetine treatment alone, a double iodide of emetine and bismuth has been recommended. This is formed by the precipitation of soluble emetine salts with Dragendorff's reagent. The drug should be given by mouth, enclosed in a gelatin capsule, paper cachet or in salol-coated pills, in doses not exceeding 3 gr. (0.2 gm.) a day for twelve successive nights. During the twelve-day course of treatment the patient should remain in bed and be given a liquid diet. Nausea and vomiting, and even slight purging, sometimes occur after its administration. The nausea and vomiting may be often prevented if 10 to 15 minims (0.6 to 1 c.c.) of tincture of opium are given previously. In the alkaline juices of the intestine the emetine is gradually liberated from the preparation, and it is important that the preparation should not be made into a hard tablet or pill. Jepps found that liquid paraffin makes an excellent excipient, 3 gr. being dissolved in ½ ounce of liquid paraffine. If dropped into a glass containing 2 to 3 ounces of water the dose was easily taken. Given by this method unpleasant results followed only in 10 of 75 cases treated, and only 12 per cent. out of a large series relapsed. Rennie concludes that the best form of administering the drug is as loose powder in gelatin capsules. If after the administration of 12 gr. of emetine bismuth iodide the examination of the feces shows that the patient is still infected he may, after an interval of a few days, be given a double course of treatment, that is, 3 gr. daily for twenty-four consecutive days, provided that no unfavorable symptoms appear.

Emetine periodide, prepared by Martindale, contains 38.7 per cent. emetine and 61.3 per cent. iodine. It is given in capsules in doses of 2 gr. (0.13 gm.), three times daily, with 5 gr. (0.3 gm.) of fel bovis which is said to increase the absorption. It is regarded by Wilmore as equal if not superior to emetine bismuth iodide. He states that it is much less toxic, and is not liable to be followed by nausea and vomiting, cardiac or muscular weakness and depression. Wilmore gave it in an intensive fifteen days' course of treatment totalling 90 gr., and claims that patients were cured who had proved refractory to emetine bismuth iodide. Manson-Bahr believes that the drug is more easily tolerated, but is much less efficacious than emetine bismuth iodide in a chronic infection.

Yatren is a combination of 20 per cent. iodine with oxyquinolin sulphonic acid, together with about 20 per cent. sodium bicarbonate, and has been recommended for the treatment of amœbic dysentery and other affections of the colon. The drug has been given in rectal injections and orally. It is rapidly absorbed and is to a great extent excreted

in the urine. If the absorption of the solution is taking place satisfactorily it can be demonstrated by means of the oxychinolin test, a green color being obtained when iron perchloride is added to the urine.

Bax, who has employed yatren orally, considers it superior to all other preparations. He gives the drug in 3-gm. doses daily in cachets for ten consecutive days, the patient remaining in bed upon a milk diet, and the second course in seven days. Gordon and Lichtenstein have reported less favorable results with this preparation.

The use of *bismuth subnitrate* has been strongly advocated especially by Deeks who recommends its use in large dosage. He gives a heaped teaspoonful, equivalent to about 180 gr. by weight, mechanically suspended in almost a tumbler of plain, or better effervescent, water, every three hours, night and day in severe cases, only lessening the amount when improvement takes place. The mechanical suspension in a large amount of water is essential, as otherwise it may form a paste or solid mass, lessening its effect. When the stools begin to lessen in number and the tongue becomes clean the number of doses is lessened to three or four daily. In very chronic cases he believes it wise to continue one or two doses daily for a month after convalescence is established. James has since advised the giving of the bismuth in these doses combined with emetine to the point of physiological reaction.

Connor, in Panama, has also had exceptional success with the combined emetine and bismuth subnitrate treatment in more than 100 amœbic dysentery cases, only 1 of which relapsed. After a preliminary purging with castor oil large doses of bismuth subnitrate are given to check the diarrhœa. The emetine is then given in four treatments, three to five days apart in severe, less frequently in mild, infections. The customary dose is 1 gr. (0.06 gm.); the average per patient, 8 to 10 gr. In addition, a normal saline irrigation was given twice daily when there was evidence of an extensive colitis.

Other preparations which have been recommended for the treatment of amœbic dysentery are chapparo amargoso and kosam (preparations from simarubaceous plants), oil of chenopodium, arsphenamine, benzyl benzoate, tannin, epinephrine, uzara, conessine and amibiasine. While favorable reports have been made on the use of these preparations, their use has not become extensive and it has not been demonstrated that any of them are equal or superior to the preparations already mentioned.

Stovarsol (acetyl-oxy-amino-phenyl-arsenic acid) has recently been recommended for the treatment of the disease. It is said to contain 27.2 per cent. of arsenic and to have slight toxicity. Marchoux found that cysts of *Entamœba histolytica*, which had persisted after a full course of emetine treatment, disappeared after the doses of 4 gr. (0.26 gm.) of stovarsol twice daily. In refractory cases he advises 4-gr. doses every second day for two months. Others report good results, some when emetine is given also.

Local Treatment.—Cases with extensive lesions of the colon which do not yield to treatment with emetine, and in which the symptoms of dysentery are not very acute, are often favorably affected by treatment

with irrigations of the large intestine. Their purpose is the flushing out of the colon and cleansing the surface of the lesions, as well as the destruction of the amœbæ. Obviously when the ulcerations are in the lower part of the colon the results of the local treatment are particularly favorable. The solution should be allowed to enter slowly by gravity, and the tube should be passed as high as possible. The amount injected is usually between 1 and 2 litres. Rectal injections of quinine sulphate or quinine muriate, 1 to 1000 or 1 to 2500, are recommended. Quinine has amœbacidal properties, and sometimes cases yield to such treatment that have not been benefited by other treatment. Solutions of silver salts have also been employed. As the flushing out of the colon often aids in the treatment, normal saline solution may at times be substituted for the quinine solution, particularly if the latter causes irritation.

Van der Togt has attempted to destroy amœbæ by increasing the osmotic tension in the bowel contents to a degree harmful to the parasites. For this he uses enemata of 20 to 40 per cent. cane sugar solution, given twice daily for eight consecutive days. Muhlens and Menk recommended the employment of yatren in enemata, which they advise should be given daily for eight to fourteen days, and after a week's interval a repetition for from three to seven days, and after another equal interval a further course for from three to five days. The drug was also given by the mouth in 1 gm. doses three times a day. When the drug is employed in rectal injections a voluminous water enema is first given to clear out the bowel. Then 200 cc. of a 2.5 to 5 per cent. yatren solution are injected at body temperature. If the process is located high up in the bowel 400 cc. of a 1.5 to 3 per cent. solution should be administered. Birt considers the best results obtained by enema in 10 per cent. solution in quantities of 100 cc. daily.

For chronic cases which do not yield to treatment the operation of appendicostomy has been suggested. Following this a catheter is inserted in the opening and the large intestine irrigated with a 1 per cent. solution of bicarbonate of soda to wash away the mucus; later a boric acid solution has been employed. Such a method is particularly recommended by Stitt and by Smits. Smits also employs for irrigation dilute silver nitrate solution following the soda solution. Some believe that cecostomy furnishes a better means of irrigation and of giving the colon rest. On the other hand, Ross states that appendicostomy did not give encouraging results during the World War, and Phillips points out that its success has not been very great in many cases. Madden believes that probably equally good results can be obtained by the systematic flushing out of the colon by the rectum. The use of the sigmoidoscope is an aid in treatment. When ulcers exist in the rectum local treatment with astringent or antiseptic substances may be applied.

Treatment of Complications.—*Amœbic inflammation* of the liver in any degree short of an actual abscess, almost certainly yields to treatment with emetine. Many writers have pointed out that in the great majority of cases of hepatic amœbiasis operative measures are unnecessary, as if

the collection of pus in the liver is not too extensive emetine alone will bring about its absorption. LeNoble and Jegat have verified the presence of pus in the liver by aspiration and have watched its absorption following emetine therapy. Fry[1] described 2 cases of large abscesses of the liver in which the diagnosis was sustained by roentgen-ray examination, in both of which all signs disappeared after 12 gr. of emetine. Rogers and many other authors believe that liver abscess can be prevented if emetine is promptly administered, and that in the presuppurative stage of amœbic hepatitis the symptoms will usually rapidly disappear under the influence of this drug. Most observers, however, believe that when a large abscess has once formed operation is advisable. It is often necessary to make exploratory punctures in order to locate the abscess, and often many punctures in different parts of the liver must be made before the abscess is found. While fatal hemorrhage has sometimes followed such punctures, Madden[2] states that he has never seen any untoward happenings, although he emphasizes that the punctures must be made with aseptic precautions and with due attention to anatomical knowledge and surgical principles. He lays emphasis on the fact that pus must be found with the needle, and that it is not customary to go on with an operation unless pus is forthcoming.

The aspiration of large amounts of pus from the liver, as first suggested by Rogers, has gained a number of adherents for its obvious advantages over the open operation. Should aspiration fail to remove the pus, operation is resorted to and emetine injections are continued until symptoms no longer persist. Manson-Bahr, Low, Pratt and Gregg[3] report a series of 15 consecutive cases without a death, all treated with aspiration, emetine, and emetine bismuth iodide. Aspiration is a simple matter, and can be performed when the patient is too ill to admit of a major operation, and to the necessity of a general anesthetic. Thurston[4] reported a series of 64 cases, 49 of which were treated by aspiration alone, of which 40 recovered and 9 died. Of the 49, 28 were aspirated once with 4 deaths, 12 were aspirated twice with 3 deaths, 7 were aspirated three times with 1 death. Adequate treatment with emetine is regarded as important as the operation. Cases in which the abscess cavity has become secondarily infected should be drained by the open operation.

Lung abscess requires the usual treatment with emetine. Abscesses which are discharging freely from the lung are often much benefited and may require no active surgical procedure. Bronchoscopic drainage and treatment should be useful. In case the pus is not being freely discharged a careful search must be made for the abscess cavity in the liver which should be drained when found. Roentgen-ray examination may give information as to the advisability of surgical intervention for the better drainage in cases where the liver abscess has ruptured into

[1] *Indian Med. Gaz.*, 1924, **59**, 488.
[2] Byam and Archibald's *Practice of Medicine in the Tropics*, London, 1923, **3**, 2509.
[3] *Lancet*, 1923, i, 941.
[4] *Lancet*, 1924, p. 1008.

the lung. If the abscess has opened into the pleura, or empyema has resulted, resection of the ribs may be necessary to secure free drainage.

For the treatment of *brain abscess*, in addition to emetine, extensive trephining is advisable and the abscess should be sought for with a channeled sound and not with an aspiration needle, owing to the viscosity of the pus. When the abscess is localized it should be opened, but a favorable result cannot be expected from operation. Morphine and bromides are indicated for the relief of headache and other cerebral symptoms.

Postcolic abscesses and amœbic abscesses in other organs, such as the spleen or ovary or Fallopian tube, as well as in the skin and adjacent tissues, may require surgical treatment. Rogers recommended in the treatment of spleen abscess repeated aspiration and injection of emetine into the cavity.

General peritonitis or *perforation* of the bowel sometimes demands surgical aid if the condition of the patient warrants it, but when one ulcer has perforated others are very likely to do so also. Patients with perforation sometimes recover without operation by the formation of adhesions. It is only in exceptional cases and before peritonitis has become pronounced that any hope of recovery can be expected. The bowel wall is frequently friable and unsuitable for suture. Local peritonitis without perforation requires rest and the application of ice or hot fomentations, with opiates by the mouth. For serious *intestinal hemorrhage* complete rest is demanded. Morphine should be given freely and ice may be applied locally. Epinephrine in doses of 1 c.c. of a 1 to 1000 solution has been recommended, and the injection of blood serum is sometimes of benefit.

In connection with *amœbic appendicitis*, the surgeon should bear in mind that when the appendix is ulcerated the cecum is usually also extensively ulcerated, and that the symptoms are more often due to conditions in the cecum.

Treatment of Carriers.—The presence of cysts of *Entamœba histolytica* in the feces of healthy individuals has been discussed. Where proper disposal of human feces is carried out the individual who harbors cysts of *Entamœbæ histolytica* in the intestine cannot be regarded as a menace, and hence his treatment from the standpoint of public prophylaxis is not justifiable. Moreover, such infections have been known to exist over long periods without the slightest symptoms, and individuals known to be carriers during life who have succumbed to other diseases have shown no gross lesion of the intestine at autopsy. It is often difficult to rid the individual of the cysts of *Entamœba histolytica* by any known method of treatment. In a large series of cases of amœbic infection some are always found to be refractory. Hence in countries where amœbic dysentery does not prevail it would seem to be more advisable to continue to observe such individuals at intervals rather than submit them to frequent treatment, and even in some countries where the disease occurs more commonly this would seem to be the wisest course. LeNoir and DeFossey have suggested rendering the intestinal conditions

such that the amœbæ do not encyst or that those which have encysted excyst. For this they recommend the administration of dried bile or of bile extract preparations. When such preparations are given in doses of 0.6 gm. per day, three times a day, in capsules, it is stated a diarrhœa results, and the stools are found to contain the vegetative forms of amœbæ as well as the cysts. LeNoir and DeFossey suggest that eliminative treatment should then be begun promptly with emetine, as the young amœbæ are less resistant than the cysts. The writer believes that a more conservative and expectant attitude should prevail in the persistent treatment of carriers who have never had symptoms of amœbic enteritis or dysentery, and who are passing only cysts of *Entamœba histolytica* and not vegetative forms.

CHAPTER XI

THE MALARIAL FEVERS

By CHARLES F. CRAIG, M.A., M.D.

Definition.—By the term malarial fevers we mean a group of specific infectious fevers due to infection of the red blood corpuscles of man by closely related animal parasites belonging to the *Sporozoa*, genus *Plasmodium*.[1] These fevers occur epidemically or endemically and are accompanied by a symptom complex which is more or less characteristic of each variety. Periodicity is one of the most marked clinical phenomena and is due to the sporulation of the plasmodia. All malarial infections are transmitted by mosquitoes of the family *Anophelina*, and so far as is known, this is the only means of transmission.

Geographical Distribution.—There is no infectious disease which can compare with the malarial fevers in the extent of its geographical distribution. In the eastern hemisphere malarial infections do not occur above 62° N. Latitude, while in the western hemisphere they are very rarely found above 45° N. Latitude. They are most common and severe in low-lying coast regions, mountainous countries being comparatively exempt. The deltas of large rivers, especially of tropical countries, are hot-beds of malarial disease, and this is also true of all bodies of water in such localities. As the equator is approached we meet less often with the benign forms of malarial infection, the prevailing types being the severe and often fatal estivo-autumnal infections. The most important malarial localities are the following:

North America.—Malaria occurs rarely above the forty-fifth parallel, but is often frequent and fatal in the Southern States and in the West Indies, especially in Cuba, as well as in Central America. In the New England and Middle Atlantic States the benign forms are present, but are comparatively rare. The severe forms prevail along the low regions of the southern coast line, and especially in the swampy regions of the Gulf States. These infections are common and severe along the Mississippi River and its southern branches, and are present in many of the Western States, especially in the river valleys of California, where severe estivo-autumnal infections are not uncommon. The regions about the Great Lakes are almost free from malaria except in certain localities about Lake Michigan. Canada is the only country in North America which appears to be almost entirely free from malaria.

[1] The malarial parasites belong to the *Sporozoa*, sub-order *Hæmosporidia*, genus *Plasmodium*. The name *Plasmodium* was given by Marchiafava and Celli, and is unfortunate from a biological standpoint. Grassi suggested the name *Hæmamœbæ* for the parasites, and this is a preferable term to *Plasmodium*, but the latter has to be retained because of the law of priority. The same objection may be raised to the name "malaria," which means bad air. With our present knowledge the name is erroneous, but is retained as it has become so firmly established.

South America.—Severe types of the disease are common, especially along the coast regions of Columbia, Venezuela, Guiana, Brazil, Ecuador, Peru, and Chile. The whole Atlantic coast line of Central America is severely infected with estivo-autumnal malaria and the most pernicious forms are common. These infections also occur along the Pacific coast line although to a lesser extent. Panama is a hot-bed of estivo-autumnal malaria but the Canal Zone is comparatively free due to the efforts of American sanitarians.

Europe.—Malarial fevers occur but rarely in England, Germany, and France. In Germany they occur along the coast of the Baltic, especially in Prussia, and they are not uncommon in the swamps of Hanover and Westphalia, and along the Rhine; in France these infections occur along the Loire and Rhone on the west coast; in Spain the valleys of the Tago and Guadalquivir are infected, and pernicious forms occur in all the countries bordering upon the Mediterranean; in Greece, Crete, Italy, Sicily, and Turkey, malaria is endemic; in Italy, especially, occur the most malignant forms in the regions around the Roman Campagna and the Pontine marshes, as well as in the valley of the Po; in Russia malarial infections are present in the valleys of the Volga, Dniester, Dnieper, and also in the regions bordering on the Black and Caspian Seas.

Asia.—India, Ceylon, portions of Arabia and China, and the islands of the Malay Archipelago are infected with the malarial fevers. This is also true of Asia Minor and the valleys of all the great rivers, as the Indus and Ganges. In Japan the benign infections are common in certain localities but pernicious forms are rare. Even the lofty table-lands near the Himalayas are infected with malarial fevers, and these fevers also occur in mountainous regions in the Federated Malay States. The Philippine Islands contain many endemic centres of severe malaria.

Africa.—The worst areas are along the west coast and the Senegal, Congo, and Niger Rivers, as well as the regions around the great lakes and the jungles and lake shores of Abyssinia. Madagascar, Reunion, and Mauritius Islands present the pernicious varieties of the disease. Around Delagoa Bay and along the east coast of Africa, estivo-autumnal fever is prevalent. Lower Egypt, the Soudan, the Nile delta, Tripoli, Tunis, and Algeria, all harbor these infections.

While these are the most important localities in which malarial infections are endemic, there are numerous districts in which a few sporadic cases occur, but which may at any time become endemic foci, provided certain species of mosquitoes belonging to the *Anophelinæ* are present, together with individuals harboring the parasites.

Etiology.—The bacterial origin of the mlarial infections was believed in for a considerable period of time, until in 1880 Laveran[1] described certain parasites occurring in the blood which he considered as the cause of the disease. His observations were soon confirmed by Richard, Marchiafava and Celli, Golgi, Councilman, Abbot, Sternberg, Osler, and Dock. In his original communication Laveran described three forms of the parasite. The first consisted of oval or crescentic bodies with hyaline protoplasm containing pigment, arranged either in clumps

[1] *Bull. de l'Acad. de Med.*, Paris, 1880, **93**, 644–658.

or in a wreath-like arrangement. This was undoubtedly the crescentic form of the parasite causing estivo-autumnal malaria. The second form consisted of small hyaline bodies containing pigment; and from these bodies there arose occasionally long, thin, hyaline filaments which possessed the property of motion. This form was undoubtedly the flagellated form of the estivo-autumnal parasite. The third form consisted of spherical, slightly granular bodies, with motionless pigment, which were evidently degenerative forms of the two foregoing classes. Richard[1] later described the intracorpuscular hyaline parasites and the segmenting bodies. In 1885 Marchiafava and Celli[2] described carefully the hyaline and intracorpuscular parasites, and proposed the name *Plasmodium malariæ*. In the same year, Golgi[3] proved that quartan fever depended upon a specific parasite, and shortly afterward differentiated the parasite causing tertian fever. To him we also owe the discovery that the malarial paroxysm always coincides with the segmentation or sporulation of a group of parasites. In 1885 Golgi also called attention to the probably distinct type of the crescentic and ovoid forms, and Councilman first called attention to the diagnostic value of the various forms observed in the blood. In 1889 Golgi showed that the crescents arose from the small, cellular rings, and that this parasite was associated with fever of a remittent character. To him belongs the credit of first clearly differentiating the estivo-autumnal parasite.

Classification.—The classification of the parasites causing malaria has occupied the attention of zoölogists for many years, and a great many different opinions have been advanced regarding their exact position. At the present time it is conceded by all that they belong to the *Sporozoa*, and the classification adopted by nearly all authorities is the one followed in this contribution. All the plasmodia of man are placed in the suborder *Hæmosporidia*, and are divided into the following species: *Plasmodium vivax* (tertian parasite), *Plasmodium malariæ* (quartan parasite), and *Plasmodium falciparum* (estivo-autumnal parasite). The Italian authorities, together with many investigators who have studied malaria in the tropics, have made a subdivision of the estivo-autumnal parasite into two varieties, the quotidian and tertian. Much labor has been expended in differentiating these varieties of the estivo-autumnal parasite, and it is undoubtedly true that they can be differentiated when the material is available for study. The writer is satisfied that the quotidian and tertian estivo-autumnal parasites can be as easily differentiated as the tertian and quartan. For the parasite causing the quotidian type of estivo-autumnal fever I have proposed the name *Plasmodium falciparum quotidianum*, considering it a subspecies of *Plasmodium falciparum*. In addition to these species a subspecies of *Plasmodium vivax* has been described, termed *Plasmodium vivax minutum*, and another species, closely resembling *Plasmodium falciparum*, and called *Plasmodium tenue*, has been described by Stephens.

The malaria plasmodia are found in man within the red-blood corpuscles and are essentially parasites living upon and within these cells.

[1] *Gaz. Med. de Par.*, 1882, **20**, 252. [2] *Fortschrite der Med.*, 1885, **3**, 787.
[3] *Arch. per le scienz Med.*, 1886, **10**, 109–135.

They destroy the red corpuscles and produce the anemia peculiar to malarial fever, together with the pigmentation, or melanemia, due to the destruction of the hemoglobin of the red cell. In describing these parasites two life cycles must be considered: First, the human cycle, *schizogony*, or asexual cycle, occurring within the infected individual, and second, the mosquito cycle, *sporogony*, or sexual cycle, occurring within the infected mosquito. These fevers are not infectious from patient to patient except through the intermediation of certain mosquitoes.

Plasmodium Vivax—(The Tertian Parasite)—(Schizogony, Human Cycle).—The tertian parasite, or *Plasmodium vivax*, appears first within the red cell in schizogony as a small actively amœboid hyaline body, the *schizont*, of various shapes, the difference in outline being due to the rapidity and extent of the amœboid movement. At first the outline of the organism is very indistinct and careful examination is needed to distinguish it. As the organism grows older and becomes pigmented it is much more easily distinguished. The hyaline stage is quickly followed by the appearance of a few minute granules of reddish-brown pigment situated within it and showing active movement. This movement is due to protoplasmic currents within the parasite. In the beginning, occupying but a minute portion of the red cell, as it continues to grow, the parasite encroaches more and more upon the infected corpuscle, until when full-grown it fills the entire cell. The growth of the parasite is gradual, covering forty-eight hours. The full-grown parasites have a rather distinct outline and the red cells containing them are greatly swollen, sometimes to almost double the size of the normal red-blood corpuscle. Toward the end of thirty-six hours the organism has approached nearly to its full growth, only a narrow rim of the red cell showing around it. Amœboid motion has become almost entirely lost, the parasite being circular in shape, well-defined, the pigment more or less motile and much increased in quantity, still, however, finely granular in appearance and reddish-brown in color. At the end of forty-eight hours *segmentation* takes place the pigment becomes collected at the centre or to one side of the organism in the form of a compact clump and fine radial divisions are noticed branching from the centre toward the periphery of the organism, dividing the parasite into small ovoid segments. As a rule, there are two rows of these segments, one row surrounding the centre, and another surrounding the first row, but very often the segments are irregularly arranged, and they are always devoid of pigment. They vary in number from twelve to twenty-four, the average being about sixteen, and are known as *merozoites*. At the time that segmentation occurs the infected red cell has apparently disappeared, being entirely destroyed by the invading parasite. The destruction of the red cell, which is complete at the time of segmentation, liberates the segments, or *merozoites*, which are capable of infecting new corpuscles, and thus the human life cycle or schizogony continues. The pigment, which is not present at the beginning of the life cycle in the red-blood corpuscle, gradually increases as the degeneration of the red cell continues, being derived from the destroyed hemoglobin of the cell. In all the pigmented forms of the tertian parasite the pigment is generally motile.

In examining blood from tertian cases it will be noticed that a certain proportion of the full-grown parasites do not segment, and it is these which are intended to commence the life cycle of the organism in the mosquito, which will be described later.

The malaria plasmodia, when stained with Wright's stain, are very characteristic. The protoplasm stains a robin's egg blue while the chromatin of the nucleus stains red or violet. In stained preparations the earliest stage in the development of *Plasmodium vivax* appears within the red-blood corpuscle as a ring of blue-stained protoplasm having upon one portion of its periphery, or within it, a spherical dot of red or violet chromatin, the interior of the ring staining as does the cytoplasm of the red-blood corpuscle, a brownish-pink or pink. As growth continues the ring-form is lost and the plasmodium appears as an irregular body stained blue and containing greenish-black pigment and fine granules or delicate strands of red or violet material, the chromatin of the nucleus. Just before segmentation this chromatin becomes collected into several more or less regular masses throughout the blue-stained cytoplasm of the parasite, while at the time of sporulation the chromatin, stained red or violet, is collected into several oval or spherical masses, each surrounded by a small amount of blue-stained cytoplasm. These bodies are the spores or *merozoites*. The infected red-blood corpuscle is much enlarged during the later stages of the growth of the plasmodium and often contains pink granules, resembling eosinophilic granules, which are known as Schüffner's dots or granules, and which are quite characteristic of infection with this plasmodium, although similar dots occur in the infected corpuscles in infections with *Plasmodium vivax minutum*.

Plasmodium Malariæ—(The Quartan Parasite)—(Schizogony, Human Cycle).—The organism appears at first within the red corpuscle as a small actively amœboid hyaline body without pigment, the *schizont*. The amœboid motion is less marked than in the tertian organism. The quartan parasite rapidly becomes pigmented, the pigment being collected in larger granules than in the tertian parasite, being less motile and arranged around the periphery of the organism, whereas in the tertian parasite the pigment is distributed throughout the protoplasm. The outline of the organism is also much more distinct than in the tertian parasite during all stages of its growth. Instead of the swollen decolorized red cell seen in the tertian infection, the infected corpuscle in quartan fever is normal in size and often slightly below normal, and darker green in color, instead of pale. This difference at once distinguishes the two species upon microscopic examination of the blood. The parasite slowly increases in size, and in doing so becomes less amœboid. The pigment increases in quantity and becomes collected at the extreme periphery of the organism and is absolutely immotile. The granules of pigment are considerably larger than in the tertian parasite, darker in color, and at no stage do they collect in small clumps throughout the protoplasm, as is common in the tertian form. As growth increases the parasite tends more and more to fill the infected red cell, and when full-grown at the end of seventy-two hours, it almost fills the cell, a small greenish rim of hemoglobin still being visible around the organism.

EXPLANATION OF PLATE II.

PLASMODIUM FALCIPARUM (TERTIAN ESTIVO-AUTUMNAL PLASMODIUM).

Stained by Wright's modification of the Romanowsky method.

FIG. 1.—Sporozoite, just attached to an erythrocyte.

FIG. 2.—Young schizont, the so-called "ring-form."

FIG. 3.—Double infection of erythrocyte by two young schizonts, or "ring-forms."

FIG. 4.—Fully developed "ring-form" of the tertian estivo-autumnal plasmodium.

FIGS. 5, 6, 7, and 8.—Developing schizonts of Plasmodium falciparum, showing increase in size, development of pigment, and division of the nuclear chromatin.

FIG. 9.—Pre-sporulating stage of Plasmodium falciparum.

FIG. 10.—Sporulating schizont of Plasmodium falciparum. Note absence of Schuffner's "dots" in this infection.

FIG. 11.—Macrogametocyte, or female gamete of Plasmodium falciparum. The so-called crescent form.

FIG. 12.—Microgametocyte, or male gamete of Plasmodium falciparum.

PLASMODIUM FALCIPARUM QUOTIDIANUM (QUOTIDIAN ESTIVO-AUTUMNAL PLASMODIUM).

Stained by Wright's modification.

FIG. 1.—Sporozoite just attached to the erythrocyte.

FIG. 2.—Young schizont, or "ring-form." Note very minute size.

FIG. 3.—Triple infection of the erythrocyte, with "ring-forms" of the quotidian estivo-autumnal plasmodium.

FIG. 4.—Fully developed "ring-form" of the quotidian species.

FIGS. 5, 6, 7, and 8.—Various stages in the growth of Plasmodium falciparum quotidianum, showing increase in size, development of pigment, and division of the nuclear chromatin.

FIG. 9.—Pre-sporulating schizont of the quotidian estivo-autumnal plasmodium.

FIG. 10.—Sporulating schizont of Plasmodium falciparum quotidianum. Note minute size of the spores, or merozoites, and the large amount of erythrocyte still preserved. In both estivo-autumnal infections note the absence of enlargement of the erythrocyte, and of Schuffner's "dots," or granules.

FIGS. 11 and 12.—Female and male crescents of this species. Note small size.

GAMETES OF TERTIAN AND QUARTAN PLASMODIA.

FIG. 1.—Young microgametocyte of Plasmodium vivax.

FIG. 2.—Well-developed microgametocyte of Plasmodium vivax.

FIG. 3.—Young macrogametocyte of Plasmodium vivax.

FIG. 4.—Fully developed macrogametocyte of Plasmodium vivax.

FIG. 5.—Flagellated microgametocyte of Plasmodium, the flagella constituting the microgametes.

FIG. 6.—Young macrogametocyte of Plasmodium malariæ.

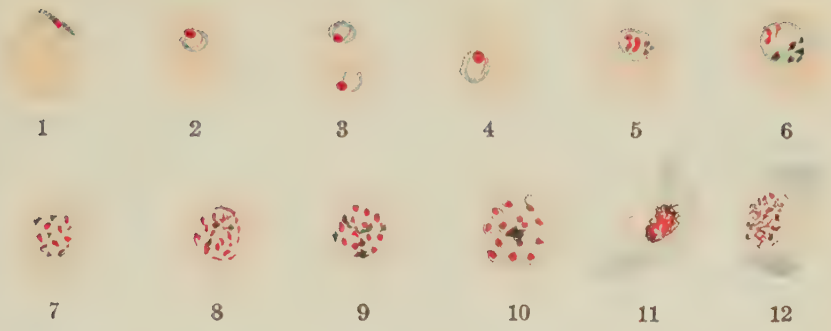
FIG. 7.—Developed macrogametocyte of Plasmodium malariæ.

FIG. 8.—Young microgametocyte of Plasmodium malariæ.

FIG. 9.—Fully developed microgametocyte of Plasmodium malariæ.

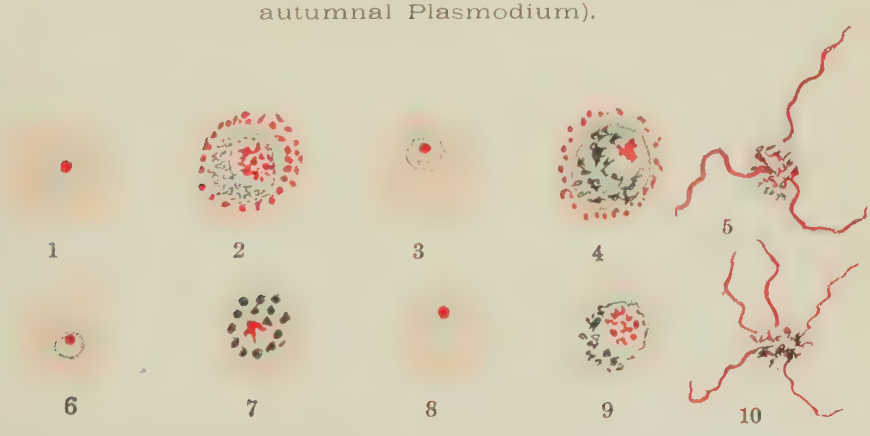
FIG. 10.—Flagellated microgametocyte of Plasmodium malariæ, the flagella being the microgametes. Note the lighter staining of the male, or microgametocytes, and the different arrangement of the nuclear chromatin.

PLATE II



Plasmodium Falciparum (Tertian Estivo-autumnal Plasmodium).

Plasmodium Falciparum Quotidianum (Quotidian Estivo-autumnal Plasmodium).



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Gametes of Tertian and Quartan Plasmodia.

At this stage the parasite is very distinctly outlined and much more refractive than the tertian species; the pigment is absolutely motionless and collected around the periphery; the shape is circular and amœboid motion has entirely ceased. At the end of seventy-two hours segmentation occurs, the pigment becoming collected at the centre or in a star-like arrangement distributed from the centre. Radial striations appear dividing the organism into from eight to twelve segments, or *merozoites*. The segments are generally arranged in a perfectly symmetrical manner around the central pigment, giving the so-called daisy or "Marguerite" appearance to the parasite. When segmentation is complete, each merozoite becomes free in the blood plasma and, in the human life cycle, again invades the red corpuscles. As in the tertian form, certain parasites do not undergo segmentation, and these are the ones intended to carry on the life cycle in the mosquito.

The staining reactions of *Plasmodium malariæ* are similar to those of *Plasmodium vivax*, but there is no enlargement of the infected red-blood corpuscle and Schüffner's dots are not present in the cytoplasm of the infected blood corpuscle. With this exception the various stages in the life cycle of the schizont present the same appearances as similar stages in the life cycle of the schizont of *Plasmodium vivax*, except that the plasmodia are more regular in shape. The schizont is smaller than that of *Plasmodium vivax* and the number of merozoites, or spores, varies from six to twelve, the structure in the stained specimen being the same.

Plasmodium Falciparum—(Estivo-autumnal Parasite)—Tertian Form (Schizogony, Human Cycle).—The writer believes with Marchiafava and Bignami that there are two distinct varieties of the estivo-autumnal parasite, the tertian and quotidian. These are distinguishable microscopically and the symptoms produced by them are characteristic and easily differentiated clinically, In previous contributions[1] the differential points between these two varieties and the clinical phenomena which are produced by them have been described.

The tertian estivo-autumnal parasite appears first within the infected red cell as a round hyaline ring or disk. The infected corpuscle is greenish in color, smaller than the normal corpuscles, and generally crenated. The young parasites are considerably larger than the quotidian parasite, occupying from one-fourth to one-third of the total area of the infected cell. The ring forms are irregular in outline, one portion of the ring being larger, giving it the so-called "signet-ring" appearance. The organism is very highly refractive and sharply outlined, appearing as though it had been cut into the corpuscle with a punch. Amœboid motion is present, although it is less rapid than in the quotidian form, and only very rarely is more than a single parasite seen within one corpuscle. In from twenty to twenty-four hours the hyaline forms become pigmented, the pigment occurring in the form of very fine, reddish-brown granules somewhat resembling those found in the tertian parasite. The pigment

[1] *The Philadelphia Med. Jour.*, April 7, 1900; also, *Jour. Am. Med. Assn.*, November 3, 1900; *The Estivo-Autumnal (Remittent) Malarial Fevers*, Wm. Wood & Co., 1901; *International Clinics*, vol. 3, 13th series, October, 1903; *The Malarial Fevers, Hemoglobinuric Fever, and the Blood Protozoa of Man*, Wm. Wood & Co., 1909; *Am. Jour. Trop. Med.*, 1921, 2, 57.

EXPLANATION OF PLATE III.

PLASMODIUM VIVAX (TERTIAN PLASMODIUM).

Stained by Wright's modification of the Romanowsky method.

FIG. 1.—Young schizont, the so-called "ring-form."

FIG. 2.—Slightly older schizont.

FIG. 3.—Double infection of red corpuscle with schizonts. Note the presence of Schuffner's dots.

FIGS. 4, 5, and 6.—Young pigmented forms of the tertian schizont.

FIGS. 7, 8, 9, and 10.—Tertian schizonts showing the division of the chromatin of the nucleus, enlargement of the infected erythrocytes, and increase in the amount of pigment.

FIG. 11.—Pre-sporulating tertian schizont.

FIG. 12.—Sporulating tertian schizont.

FIG. 13.—Free spores, or merozoites, of Plasmodium vivax.

FIG. 14.—Microgamete of Plasmodium vivax.

PLASMODIUM MALARIÆ (QUARTAN PLASMODIUM).

Stained by Wright's modification.

FIG. 1.—Young schizont, or so-called "ring-form."

FIG. 2.—Double infection of erythrocyte, with quartan schizonts.

FIGS. 3 and 4.—Young pigmented schizonts.

FIGS. 5 and 6.—Half-grown forms of Plasmodium malariæ, showing the division of the chromatin.

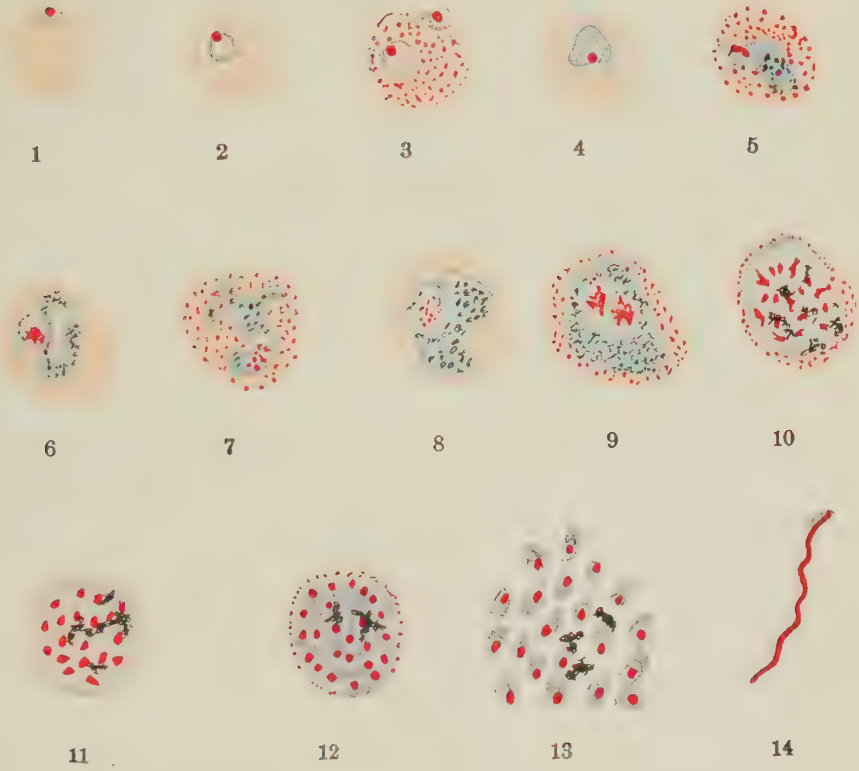
FIG. 7.—Pre-sporulating schizont of Plasmodium malariæ.

FIG. 8.—Sporulating schizont of Plasmodium malariæ. (Note smaller number of merozoites, and lack of enlargement of the erythrocyte, as in the tertian plasmodium.)

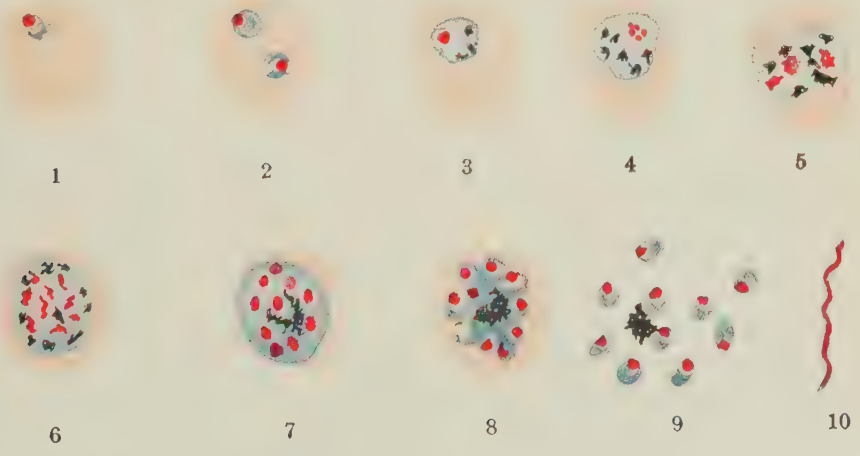
FIG. 9.—Free spores or merozoites of Plasmodium malariæ.

FIG. 10.—Microgamete of Plasmodium malariæ.

PLATE III



Plasmodium Vivax (Tertian Plasmodium).



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Plasmodium Malariæ (Quartan Plasmodium).

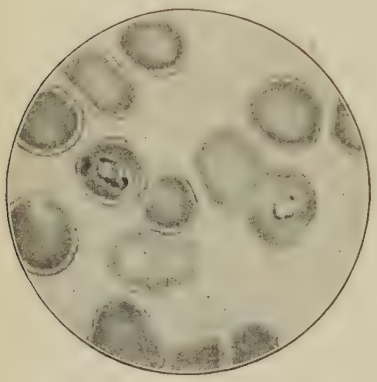
is in larger amount than in the quotidian parasite and is generally motile. As growth increases amœboid motion becomes lost, and this is also true of the peculiar ring-shape, so characteristic of this form of the parasite. At the time of segmentation, which occurs in forty-eight hours, the organism occupies about two-thirds of the infected red cell. The pigment is collected at the centre and radial striations start from this point and divide the parasite into ten to twenty-four segments, or *merozoites*. In some instances as high as thirty *merozoites* have been counted. Segmentation occurs within the red-blood corpuscles, but its situation is not so easy to distinguish in this form as in the quotidian. The segmenting forms occur but seldom in the peripheral blood, although they are very numerous in certain cases in blood from the spleen. The young segments are liberated in the blood plasma and again infect the red cell; thus the human cycle is repeated.

The staining reactions are similar to those of the other malaria plasmodia. The young schizonts, or ring-forms, show a blue-stained ring of cytoplasm containing at some portion of the periphery a spherical mass of red or violet chromatin, the portion of the ring opposite the chromatin dot being expanded, the cytoplasm at this portion being larger in amount than at any other portion of the schizont. A few minute pigment grains, stained a greenish color may be rarely observed within this expanded portion. Later stages of the schizont stain as do the other malaria plasmodia but the infected red-blood corpuscle is not enlarged and Schüffner's dots are absent. Basophilic granulation of the cytoplasm of the infected corpuscle is present, the granulations being commonly known as Maurer's dots. The merozoites stain in the same manner as the merozoites of the other malaria plasmodia but are seldom observed in stained preparations of peripheral blood.

Plasmodium Falciparum Quotidianum—(Estivo-autumnal Parasite)—Quotidian Form—(Schizogony, Human Cycle).—The *quotidian* parasite appears at first in the infected red cell as a very minute ring-shaped or round hyaline body, the *schizont*, which upon close inspection shows very active amœboid motion. The outline of the organism at first is indistinct, but gradually becomes more distinct and when full-grown it is very clear-cut and refractive. The round forms are perfectly hyaline in appearance but the ring form, which is most common, consists of a narrow hyaline body enclosing a small area which shows the normal greenish-yellow color of the infected corpuscle. This appearance is considered by most authorities to be due to the fact that the centre of the parasite is much thinner than the periphery, thus allowing the normal color of the corpuscle to show through. Careful observation of these ring forms, however, will show that they often become perfectly hyaline and in so doing the protoplasm of the organism flows in from the edge of the ring, thus tending to prove that no protoplasm existed in this greenish-colored area. The amœboid motion is very active but the organism has to be carefully watched to distinguish it. The infected red corpuscle is generally smaller in size than the normal corpuscle and darker green in color. It is very apt to be crenated. In many instances double or triple infections of the corpuscle may be

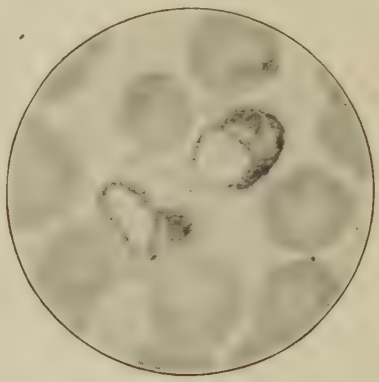
observed. In the peripheral blood the hyaline, round or ring-shaped organisms are those which are most commonly observed, although a certain number of pigmented forms are not uncommon. The pigmentation is never as marked as in the tertian or quartan parasite, the pigment consisting of a small, solid block, almost black in color, situated at some portion of the edge of the parasite or at the centre; it is never

Fig. 31



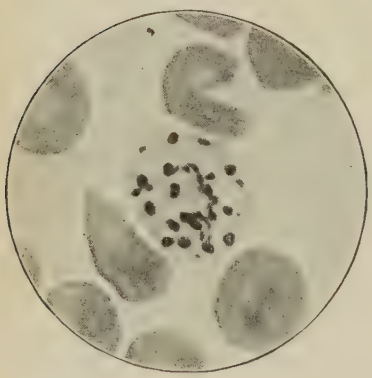
Plasmodium vivax (tertian). Ring form. × 1200.

Fig. 32



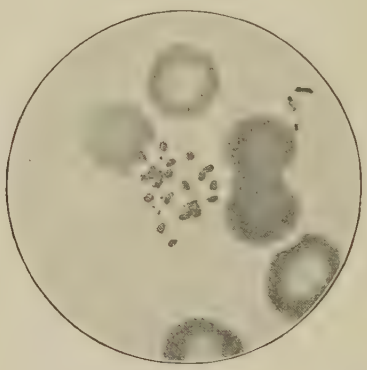
Plasmodium vivax (tertian). Half-grown pigmented form. × 1500.

Fig. 33



Plasmodium vivax (tertian). Sporulating form. × 1800.

Fig. 34



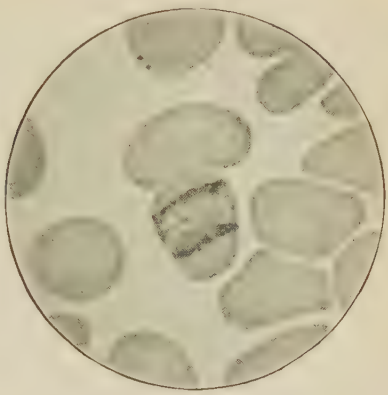
Plasmodium vivax (tertian). Free spores. × 1200.

motile. Very rarely the pigment consists of fine granules, but these never number more than three of four. The segmenting forms are very seldom observed in the peripheral blood, although blood from the spleen taken at the proper time in well-marked cases presents numerous parasites undergoing this process. Segmentation occurs at the end of twenty-four hours. Just before segmentation the parasite occupies about one-half of the red-blood corpuscle, thus distinguishing it from the quartan and

Fig. 35

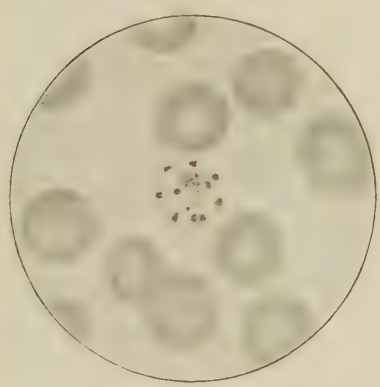
Plasmodium malariæ (quartan). Ring forms. × 1500.

Fig. 36



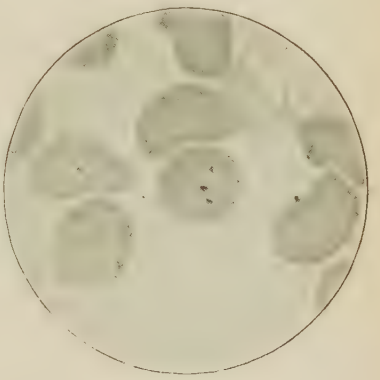
Plasmodium malariæ (quartan). Half-grown "band" form. × 1800.

Fig. 37



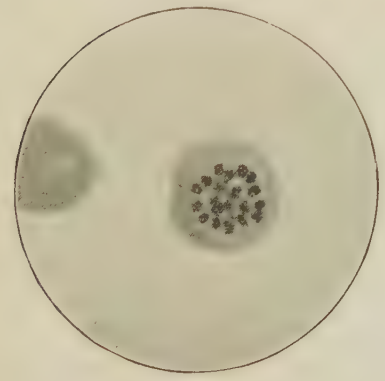
Plasmodium malariæ (quartan). Sporulating form. × 1200.

Fig. 38



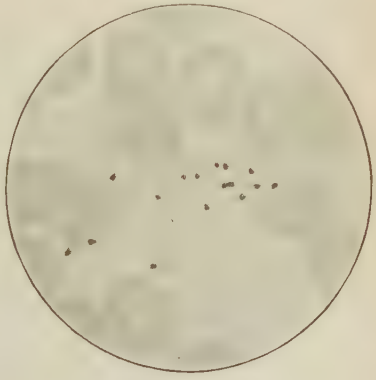
Plasmodium falciparum (tertian estivo-autumnal). Ring form. × 1500.

Fig. 39



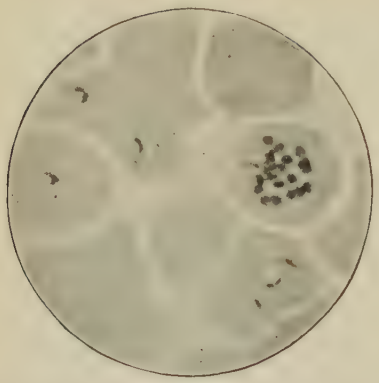
Plasmodium falciparum (tertian estivo-autumnal). Sporulating form. × 1800.

Fig. 40



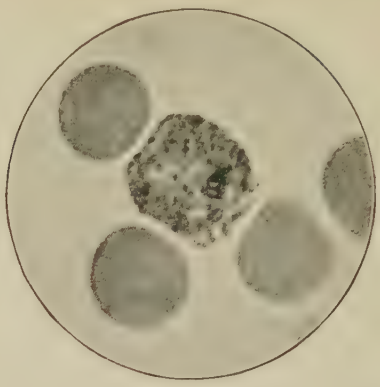
Plasmodium falciparum (tertian estivo-autumnal). Free spores. × 1200.

Fig. 41



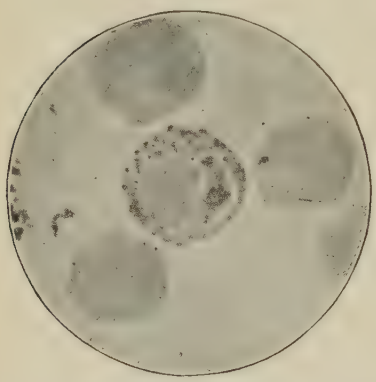
Plasmodium falciparum (quotidian). Ring form and sporulating form. × 2000.

Fig. 42



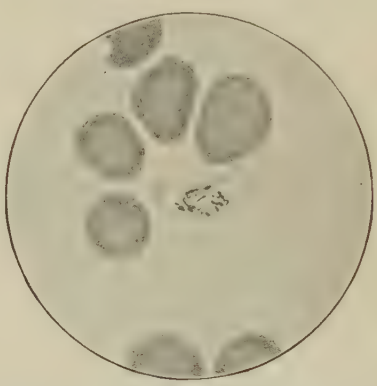
Macrogamete of Plasmodium vivax. Full-grown female gamete or macrogamete. × 1800.

Fig. 43



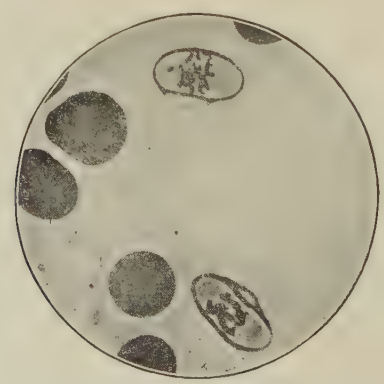
Microgametocyte of Plasmodium vivax. Full-grown male gamete or microgametocyte. × 1800.

Fig. 44



Microgametocyte of Plasmodium falciparum. Female crescent of estivo-autumnal parasite. × 1200.

Fig. 45



Microgametocyte of Plasmodium falciparum. Male crescent of estivo-autumnal parasite. × 1200.

tertian varieties which fill the corpuscle. The pigment does not show any decided increase in amount and is absolutely immotile. At the time of segmentation this pigment becomes collected at the centre of the parasite and radial striations can be detected, starting from the centre and dividing it into from six to eighteen very minute round or oval segments, or *merozoites*. While in the tertian and quartan forms it is often impossible to distinguish the remains of the red corpuscle when segmentation occurs, in this variety it can be plainly seen that segmentation occurs within the infected red cell. The merozoites are liberated by the entire destruction of the red corpuscle; each merozoite is capable of infecting a red cell and the human cycle is thus repeated.

In this variety, as well as in the tertian form, peculiar bodies occur which are developed within the red-blood corpuscle, but which do not undergo segmentation. These are the so-called *crescents*, which are so characteristic of estivo-autumnal infections, and which will be described in considering the mosquito cycle of this parasite.

The staining reactions are similar to those of other malaria plasmodia but the very minute ring-forms of this species show very little blue-stained cytoplasm and a relatively large amount of chromatin, stained a red or violet color. Often the chromatin apparently composes a large portion of the ring-shaped organism, being arranged in a semilunar mass around the periphery of the organism. The merozoites are very minute, composed largely of red or violet chromatin and a very minute amount of blue-stained cytoplasm. The sporulation bodies only fill about one-half of the infected red-blood corpuscle, which is not enlarged and is often slightly smaller than normal and crenated. Schüffner's granules are not present but the basophilic granulations of Maurer are often observed in the cytoplasm of the infected red-blood corpuscle.

Development of the Malaria Plasmodia within the Mosquito (Sporogony, Sexual or Mosquito Cycle).—As has been mentioned, in tertian and quartan infections, certain organisms occur which do not undergo segmentation. This is also true of the estivo-autumnal infections, in which a peculiar body known as the crescent appears, intended to continue the life cycle of the parasite within the mosquito.

Tertian and Quartan Forms.—In tertian and quartan infections, in blood which has been removed from the body for some time, peculiar bodies occur known as *flagellated* organisms. These are of two kinds, which the writer designated in an early contribution[1] as active and passive flagellated organisms. These forms are sexual in nature, the active flagellated body being the male, the passive the female parasite. The active flagellated organism, or the *microgametocyte*, is spherical in shape and filled with actively motile pigment, in the form of small granules distributed throughout the protoplasm of the organism. In such round bodies the pigment becomes more and more active, until finally three or more serpentine prolongations of the protoplasm appear at the circumference of the organism. These prolongations are from three to four times the diameter of the parasite, are possessed of a very active lashing

[1] *New York Med. Jour.*, December 23, 1899.

movement, and are known as flagella, or *microgametes*. With this form of the organism round bodies occur in which the pigment is collected in larger clumps and generally arranged around the circumference in the form of a perfect ring, while there is no evidence of motility. These are the passive flagellated organisms, or *macrogametocytes*, and never present the process of flagellation as seen in the *microgametocyte*, or active body. The flagella from the *microgametocyte* eventually become free in the blood plasma and sometimes can be seen attached to the *macrogametocytes*. This process, however, takes place in nature in the middle intestine of the mosquito. A distinct difference has been demonstrated in the structure of the female *macrogametocytes* and the male *microgametocytes*. In the *macrogametocyte* the nucleus is of good size and situated at one side of the centre of the organism, containing little chromatin. In the *microgametocyte* the nucleus is always situated at the centre of the organism and contains a large amount of chromatin. When the flagella, or *microgametes*, develop from the *microgametocyte*, it has been demonstrated that the chromatin passes into them and forms an essential portion of their structure. Prior to the fertilization of the *macrogametocyte* by a flagellum or *microgamete* certain nuclear changes occur in the former and when completed the *macrogametocyte* is called a *macrogamete*.

Estivo-autumnal Infections.—In the blood in these infections peculiar forms of the parasite occur known as *crescents*. These are developed within the red-blood corpuscle and are typically crescentic in shape. They are very refractive, having a more or less granular protoplasm, and contain within them, generally at the centre, but sometimes at one or the other pole, a clump of pigment arranged in the form of slender rods or minute dots. In the very young crescents the pigment is distributed throughout the protoplasm, but as the crescent matures it collects at the centre or at one end. The border of the crescent is sharply cut and is represented by a single or double line, having a peculiar greenish color. In most crescents, when full-grown, careful examination will show a dim line upon the concave side of the organism, which has a peculiar greenish color. This represents the remainder of the red-blood corpuscle in which the crescent was developed.

In *tertian estivo-autumnal* infections the crescent is much more slender and has more pointed extremities. It very seldom shows a double outline; the protoplasm is finely granular and the pigment is large in amount and in the form of slender rods. In the *quotidian estivo-autumnal* infections the crescent is generally much shorter and plumper than in the tertian. Its extremities are rounded and it always presents a distinct double outline. The protoplasm is less granular and the pigment is smaller in amount and in the form of dots. Normally in the mosquito, and also in blood removed for some time from the body, these crescents undergo a series of changes, first becoming oval in shape and finally round. The spherical bodies represent, in the estivo-autumnal infections, the *macrogametocytes* and *microgametocytes* of the tertian and quartan infections and undergo similar changes in the stomach or middle intestine of the mosquito; that is, the male elements, or *microgametocytes*, become

flagellated, the flagella, or *microgametes*, becoming free and fertilizing the female elements, or *macrogametes*. The male crescent, or *microgametocyte* in both species of estivo-autumnal parasites can be differentiated from the female crescent or *macrogametocyte* by its short, plump, kidney-like shape, the female crescent being longer and more slender in shape.

Staining Reactions of Gametes.—The staining reactions of the *gametes* of the malaria plasmodia are similar to those of the forms in the human life cycle, the cytoplasm of the *gametes* staining a blue color, with the Wright stain, and the chromatin a red or violet color. The *microgametocytes* stain much less intensely than do the *macrogametocytes* and in this way the sex of the *gametes* can be easily distinguished in stained specimens, the cytoplasm of the *microgametocyte*, or male gamete, staining a pale blue, while that of the *macrogametocyte*, or female *gamete*, stains a very deep blue color.

Cycle of Development.—Having considered the bodies which enter into the mosquito cycle, and which may be observed at times in human blood which has been removed from the body for a short time, we now take up the cycle of development which these bodies undergo in the mosquito, bearing in mind that it is essentially the same in all species of the plasmodia. The process of flagellation and the fertilization of the *macrogamete*, the female organism, by the *microgamete*, or flagellum, which occurs normally in the middle intestine of the mosquito after biting an infected individual, has been described. The result of this fertilization is known as the *sporont* or *zygote*. After a certain period of time the *sporont* becomes elongated and finally motile, and it is then known as the *oökinete*. The *oökinete* penetrates the wall of the middle intestine and eventually becomes situated on the outer side of the epithelium and the basement membrane of the intestine between the adipose tissue and the muscular wall. Here the organism becomes spherical in shape and forms a cyst known as the *oöcyst*. At this stage the protoplasm is granular and reticular in appearance, the pigment is reduced in amount, and the entire organism is enclosed within a well-defined capsule. The *oöcyst* is formed at about the third or fourth day after infection of the mosquito. About the fifth or sixth day the *oöcyst* enlarges and within it are formed spherical refractive bodies known as *sporoblasts*. At this stage the organism is increased so much in size that it projects from the intestinal wall. Besides the *sporoblasts*, the cyst contains some pigment and minute granules which resemble fat. At the end of a week the *sporoblasts* have produced a large number of delicate filaments having pointed extremities and containing a small amount of nuclear chromatin. These filaments are the *sporozoites*. They are about 14μ in length and are arranged in a ray-like formation about a central mass which may contain pigment. At this stage the capsule of the cyst is very distinct. The *sporozoites* are finally liberated by the rupture of the cyst and make their way to the tubules of the salivary glands. At this time the infected mosquito, when biting a man, will inoculate the *sporozoites*, which, penetrating the red-blood cells, develop into *schizonts*, and the human cycle of the organism begins. The entire cycle of development in the mosquito is about fourteen days in duration.

Briefly stated, the cycle of development of the malarial plasmodium in the mosquito may be summed up as follows:

1. *Macrogametocyte,* in tertian and quartan infections, the female spherical bodies, and in estivo-autumnal infections the female crescent.
2. *Macrogamete,* the name applied to the female elements after they are prepared for fertilization.
3. *Microgametocyte,* in tertian and quartan infections the male spherical bodies and in estivo-autumnal infections the male crescent.
4. *Microgamete,* the liberated flagellum of the *microgametocyte.*
5. *Sporont* or *zygote,* the result of the fertilization of the *macrogamete* by the *microgamete.*
6. *Oökinete,* the motile stage of the *sporont* or *zygote.*
7. *Oöcyst,* the cystic stage of the *sporont* or *zygote.*
8. *Sporoblasts,* developed within the *oöcyst.*
9. *Sporozoites,* developed within the sporoblasts and liberated by the rupture of the *oöcyst,* are introduced into man by the mosquito and begin the human life cycle by infecting the red-blood corpuscles.

This cycle of development has been demonstrated in the mosquito in all species of malaria plasmodia, and infection of man by the mosquito has been demonstrated with all species of plasmodia.

The Malaria Mosquitoes.—Only one subfamily of mosquitoes, so far as we know, is capable of transmitting malaria, the *Anophelina.* Several genera belonging to this subfamily contain species which have been proved to be carriers of malaria, and the following are transmitters of the disease:

United States. *Anopheles quadrimaculatus. A. punctipennis. A. pseudopunctipennis. A. crucians.*

South America. *A. albimanus. A. argyritarsus. A. cruzi. A. intermedius. A. punctipennis. A. pseudopunctipennis. A. pseudomaculipes. A. tarsimaculata.*

Panama. *A. albimanus. A. argyritarsus. A. pseudopunctipennis. A. tarsimaculata.*

Europe. *A. maculipennis. A. superpictus. A. sinensis. A. turkhudi.*

Asia. *A. barbirostris. A. culicifacies. A. funestus. A. fuliginosus. A. ludlowi. A. maculatus. A. maculipalpis. A. minimus. A. rossi. A. stephensi. A. sinensis. A. theobaldi. A. umbrosus. A. turkhudi. A. willmori.*

Africa. *A. culicifacies. A. funestus. A. costalis. A. maculipennis. A. maculipalpis. A. mauritanius. A. pharoensis. A. turkhudi. A. umbrosus.*

Philippine Islands. *A. barbirostris. A. fuliginosus. A. ludlowi. A. maculatus A. minimus. A. sinensis.*

Porto Rico. *A. albimanus. A. argyritarsus. A. tarsimaculata.*

Contributing Factors.—While the malarial parasites are the direct cause of the malarial infections, and while the transmission of the disease depends entirely, so far as we know, upon mosquitoes belonging to the *Anophelinæ,* there are certain indirect etiological factors. These favor the development of the parasites within the body or indirectly aid in infection. Among them are the following:

Locality.—This has a decided influence upon the character of the infection. The mild tertian and quartan infections, especially the tertian, are of almost world-wide distribution, but the more severe estivo-autumnal types are much more limited as regards locality, being very uncommon

in northern latitudes and becoming more and more common as the tropics are approached.

Climate.—These infections are most common and pernicious in tropical climates, so that heat may be considered as an essential predisposing cause. Even in temperate climates, the estivo-autumnal fevers prevail mostly during the summer and autumn months, while in the tropics they prevail throughout the year. Thayer and Hewetson[1] called attention to the seasonal variation in Baltimore. The smallest number of cases occurred in December, January, and February; during the spring months the cases increased until May, and then decreased until July, when they again increased and reached the maximum in September. There is no doubt that season has a most marked influence. This is due to the fact that mosquitoes, especially in temperate climates, are much more numerous in the summer and autumn months, and to the further fact that a temperature of between 72° to 86° F. is most favorable for the development of the malaria plasmodia within the mosquito.

Time of Day.—It has always been observed that there is much more danger of contracting malaria at night than during the day. This is easily explained as mosquitoes usually bite during the night.

Altitude.—These diseases occur especially in lowlands along the coast and rivers of warm countries. Mountainous regions are generally free from malaria, although not always, for in the Philippine Islands certain valleys are almost free, while the hills in the vicinity are notoriously infected. In the tropics, persons sleeping in the lower stories of houses are more apt to become infected with malaria than those in the upper stories for, as a rule, mosquitoes do not fly to any great height.

Moisture.—Marshes and low-lying damp regions are usually conducive to malaria, and moisture is an important factor. This is explained by the fact that mosquitoes are most numerous in moist regions. Rain favors the production of malaria because it favors the breeding of mosquitoes.

Soil.—Tropical jungles, low marshy islands, or lands covered with stagnant water have always been regarded as conducive to malarial infection. The soil *per se* has nothing to do with the production of malarial disease except as it favors the breeding of mosquitoes. A moist soil brings about conditions favorable for the development of the mosquito larvæ; this is also true of those instances in which malarial epidemics have followed the upturning of soil in certain localities, thus favoring the formation of stagnant pools in which mosquito larvæ develop.

Race.—According to Thayer and Hewetson, the negro is less liable to contract malaria than the white man. This subject has attracted the attention of many investigators, and it has been found that the native dark races acquire a more or less complete immunity in early life from malarial disease. A very large percentage of negro children in infected localities harbor the malaria plasmodia, but this is not as true of the adult. There is probably no racial immunity but an acquired immunity is present among many people who inhabit malarial regions.

[1] *Johns Hopkins Hospital Reports*, 1895, **5**, 5–215.

Age.—Children are more susceptible than adults, probably due to the fact that mosquitoes bite children in preference to adults.

Sex.—When equally exposed, both sexes have the same ratio of infection, but malaria is more common in men than in women, as the latter are not as often exposed to the bites of the mosquito.

Occupation.—This becomes a predisposing factor in proportion to the chances that occupation gives of infection by the mosquito. Laborers working at ditching, railway building, and occupations which necessitate the turning up of the soil and exposure to night air, and therefore to the bites of mosquitoes, are especially liable to contract malarial fever.

There are other factors, among which may be mentioned those which lower the resisting powers, such as exposure, dissipation, overeating, overwork, mental or physical, and anything which interferes with the normal physiological processes. There can be no doubt that an infection with a small number of malaria parasites is overcome, in a great many instances, by the healthy individual, but should the normal resisting powers be lowered such an infection would result in the symptoms of the disease.

Additional factors are the number of infected mosquitoes in the locality; the number of human "carriers;" the number of *gametes* in the blood of the human "carriers;" the proportion of male and female *gametes* in the blood of the "carriers;" the number of susceptible individuals; and the particular species of anopheline mosquitoes present. Variations in any one of these may have a profound influence upon the character and amount of infection in a locality.

Cultivation.—The estivo-autumnal parasites have been kept alive outside of the human body for some days. Sakharov was the first to perform such experiments and was able to keep the parasites alive in blood, obtained by leeches from the human subject, for a week. No reproductive changes were observed. The work of Bass has demonstrated that it is possible to cultivate the malaria parasites in blood to which dextrose has been added and he succeeded in thus cultivating them through four generations.

Inoculation Experiments.—The malarial fevers may be transmitted by direct inoculation from man to man. It has invariably been found that the type of parasite inhabiting the blood injected is found again in the blood of the individual infected, and is followed by the clinical symptoms of the variety of malaria produced by the type of parasite injected.

Immunity.—This may be considered under the following heads: Racial, congenital, and acquired. Natural immunity is undoubtedly rare.

Racial Immunity.—Certain races of mankind have been considered immune to the malarial fevers. This rests upon very little proof, and cannot be substantiated by facts. Some races are more resistant to malaria than others; for instance, the dark races are more resistant in adult life, but the immunity which exists is undoubtedly acquired. In other words, in those races which live in malarial localities the disease is acquired in very early life and a natural immunity is established so that the adult individuals are resistant to the infection.

Congenital Immunity.—There are people in the most malarious localities who have never suffered from the disease. This immunity is, in all probability, congenital, and in a few instances is a family characteristic.

Acquired Immunity—Long residence in a malarious country may confer a relative immunity. Repeated attacks will in time render the individual less liable to further attacks. We can explain this in only one way: That the malarial poison produces changes in the human organism which render it at least partially immune. The history of acquired immunity is of repeated attacks of malarial fever, each one a little less severe than the preceding, until at last a spontaneous permanent cure results. Such immunity may be lasting, but as a rule hardship, privation, ill-health, or removal to a new locality destroys it. The immunity thus acquired is an immunity to the toxin, or toxins, of the plasmodia, but not to the plasmodia, for individuals showing such immunity often show malaria plasmodia in their blood although no clinical symptoms of the infection are present.

Pathology.—Primarily, malarial infections exert the most marked effect upon the blood, as the plasmodia live at the expense of the red cells, and probably elaborate toxins which materially affect all the elements of this fluid. In 1847, Meckel discovered granules of pigment in the blood, and since then melanemia has been recognized as one of the most characteristic features of malarial disease. The pathological changes in the blood are the result of primary and secondary causes, the primary cause being the infection of the red cells by the parasites and the changes brought about by such infection; the secondary, the anemia which is the inevitable result of malarial infection.

Macrophages occur in the blood, containing much pigment, and, especially in the estivo-autumnal infections, numerous plasmodia. With these, either free or within many of the leukocytes, brown, black, or brownish-yellow pigment occurs as blocks, granules, rods, grains, and irregular clumps. The occurrence of this pigment is one of the most characteristic conditions in the blood of malaria. The pigment occurs in two forms, *melanin* and *hemosiderin*. The first gives no reaction for iron; the second does. As regards the origin of the two varieties Bignami has said: "The melanemia, index of an acute infection, is derived only from the direct transformation of hemoglobin into *melanin* through the action of the parasites within the red-blood corpuscles; the melanosis of the viscera, spleen, liver, bone-marrow, etc., index of a previous infection, has a double origin. In chief part it is derived from the melanemia; that is, from the disposition in the viscera of the black pigment (*melanin*) formed during the acute infection in the circulating blood; in part it has a local origin, that is, it is derived from the slow transformation of the blocks of yellow-colored pigment (*hemosiderin*), which are deposited or formed in the spleen and in the other viscera from the enormous quantity of altered red-blood corpuscles, which, in grave infections, die before the direct action of the parasites has transformed their hemoglobin into black pigment."

Besides changes in the form and color of the red cells, as well as the occurrence in the blood of pigmented leukocytes and pigment, in all forms

of malarial fever there is a reduction in both the red and white corpuscles. This reduction is very often more marked in tertian and quartan malaria than in estivo-autumnal, and is due to the action of the parasites upon the corpuscles containing them, the action of the poisonous material elaborated and set free by the parasites, and to inhibited function of the blood-producing organs.

Kelsch[1] found that a reduction followed every paroxysm of the fever. This reduction may be very great; cases have been observed in which only 500,000 red cells per c.mm. were present. In ordinary cases, after the infection has persisted for a few days, it will be found that the red cells have fallen to 2,000,000, or slightly less, per c.mm. This marked reduction, however, is not persistent, for in long-continued infections after a certain amount of anemia has been produced there is no further fall, and even in most cases a slight gain over the lowest point reached during the acute infection. In the pernicious forms the red cells may fall to 1,000,000 or less per c.mm. within twenty-four hours, but if the patient has suffered from repeated attacks such a marked decrease is seldom observed. The return to the normal number of red cells is generally rapid after the mild, and in some cases after severe infections which have been promptly stopped by treatment; but in cases treated improperly or in which many relapses have occurred, a chronic and persistent anemia is produced. In severe cases nucleated red cells are sometimes seen and poikilocytosis is almost invariably present. In such cases the polymorphonuclear leukocytes are decreased while the mononuclear are increased.

As regards the white corpuscles, in general the reduction in their number corresponds with that of the red cells. During the paroxysm there is often a leukocytosis, while between the paroxysms the leukocytes are markedly reduced in number. This is, in general, true of all forms of malarial fever, but in some cases of fatal pernicious malaria a leukocytosis is observed. Much attention has been paid to a relative increase in the mononuclear leukocytes as of diagnostic importance in malarial infection. While probably in a majority of instances there is a considerable increase in this type of cell, it has not been the writer's experience that very much weight can be given in diagnosis to a mononuclear increase, as it occurs in so many conditions not malarial in nature.

Besides the reduction in the red and white corpuscles there is generally a marked reduction in the hemoglobin, especially in the estivo-autumnal infections. This reduction may be very rapid, the hemoglobin falling from 10 to 40 per cent. within two or three days. Little weight can be given to this as regards the prognosis of individual cases. In some of the most pernicious forms there may be but a slight reduction, while in many benign tertian infections it is often very marked.

The Urine.—In many cases of benign tertian and quartan malarial infections there is but little change in the urine, but in the more severe estivo-autumnal infections there is often a marked reduction in the amount during the apyrexial stage, while during the paroxysms the amount is increased. *Polyuria* is often marked during the convalescence

[1] *Archives de physiologie*, 1875, **8**, 690.

from tertian and quartan fevers but is not so common in the estivo-autumnal infections. Sometimes the polyuria is very excessive. One patient observed by the writer, after a tertian estivo-autumnal attack, passed from 20,000 to 25,000 cc. of urine per day. The *color* is generally dark amber or reddish, and the *acidity* is increased when the urine is diminished in amount. The *specific gravity* is increased during the attack but with polyuria it is generally low, from 1.005 to 1.010. The amount of *urea* excreted in twenty-four hours is increased, especially during the paroxysm, but in cases showing polyuria the amount is generally decreased. The *chlorides* are not increased as a rule. *Albumin* appears in a proportion of very severe tertian and quartan infections and in the majority of estivo-autumnal infections. In the last, hyaline and granular *casts* are often observed, and it can be stated as a rule that all fatal cases of malaria show albuminous urine containing casts prior to death. Personal observations suggest that *indican* is almost invariably increased in the urine of patients with estivo-autumnal infections. An acute nephritis is observed in from 4 to 5 per cent. of severe estivo-autumnal infections, and in an occasional case of tertian and quartan malaria.

Morbid Anatomy.—A patient dead of malarial fever presents a peculiar brown or grayish hue of the *skin*. The emaciation depends upon the duration of the infection. Rigor mortis is moderate, and postmortem discoloration occurs early and may be very intense. As most cases of pernicious malaria die from cerebral complications, the *brain* presents most marked lesions. Externally the bloodvessels are much congested, the entire organ appearing hyperemic. Small capillary hemorrhages are often observed and œdema is the rule. If no brain symptoms have been exhibited during life, the organ externally shows but little hyperemia. The changes in the brain consist in congestion of the capillaries and minute hemorrhages within the substance of the organ. The congestion and hemorrhages are due to blocking of the capillaries by malaria parasites, which may be observed in various stages of development within the red cells, with an immense amount of pigment and numerous pigmented leukocytes. Very often the pigment is present in such large amount that the organ appears pigmented upon naked-eye inspection. The parasites may be so numerous that there are hardly any uninvaded corpuscles seen, or they may be few in number. Microscopically, it may be found that many of the capillaries in the severe infections are entirely filled with red cells containing parasites, and often thrombi are formed, composed of such corpuscles, with pigment and pigmented leukocytes. Free parasites may be observed, as well as macrophages, free pigment, pigmented leukocytes, and endothelial cells. In the nerve cells in estivo-autumnal infection, changes occur both in the protoplasm and nucleus and lead to complete degeneration. Guarnieri described the changes in the *retina* in pernicious malaria, finding hemorrhages and congestion of the capillaries, leading to impairment of function.

The changes in the *lungs* are not characteristic, varying considerably according to the stage of the disease, and being those usually found in severe fever. A microscopic examination of sections in certain cases shows congestion of the alveoli, which contain large numbers of pig-

mented, parasite-laden, white cells, and infected red cells. If bronchopneumonia has occurred, the exudation in the alveoli is mostly composed of the polymorphonuclear leukocytes, with numerous infected red cells and pigment, although the free pigment is generally small in amount. A pneumonia complicating a fatal attack of malarial infection, is without doubt due to a double infection by the pneumococcus and malaria plasmodium.

No characteristic changes are observed in the heart muscle.

There has been considerable discussion regarding the changes in the *stomach* and *intestine* in pernicious malaria. In certain cases in which diarrhœa has been marked some time before death, the mucous membrane of these organs is more or less pigmented with marked hyperemia, and even necrosis and ulceration. The Peyer's patches, as well as the solitary glands, are often swollen. Sections of the stomach and intestine show that the capillaries of the mucous folds are often crowded with parasite-invaded corpuscles and these may occlude the capillaries, resulting in necrosis and ulceration of the mucous membrane.

The *liver* is generally enlarged and markedly pigmented and in some cases almost black. The cut surface is often very much pigmented and generally greatly congested. Microscopically the most marked changes are found in the capillaries and liver cells. The capillaries show many very large phagocytes containing much pigment and sometimes infected red-blood corpuscles, as well as malaria parasites. The epithelial cells are greatly swollen and may contain free pigment and degenerated organisms. Free pigment is often observed in large lumps within the liver capillaries, while the stellate cells of Kupfer present marked pigmentation. The liver cells are atrophied, undergoing fatty degeneration, necrosis, and pigmentation. The last is not due to malarial pigment but to pigment derived from degenerated red-blood corpuscles and is not characteristic of malaria. Areas of focal necrosis occur, believed by Flexner to be due to some circulating toxic substance.

The organ which presents probably the most marked changes is the *spleen*. It is almost invariably enlarged, sometimes enormously so. It is of a dark blue or almost black color externally, the capsule being smooth. The cut surface is of a chocolate, slate, or almost black color, the consistence being very greatly decreased. The Malpighian corpuscles are almost invisible. The capillaries are found greatly congested by multitudes of red-blood corpuscles, most of them containing parasites. This is not always true, as there are numerous cases in which few infected red-blood corpuscles are demonstrable in the spleen. The intense congestion of the capillaries pushes apart the cells of the splenic pulp, and in some cases large areas are destroyed by hemorrhagic exudation. In the spleen the red cells contain parasites in all stages of development, but the pigmented forms and the segmenting bodies are most commonly observed, as well as the crescents in estivo-autumnal infections. Besides the infected red-blood corpuscles, sections show an immense number of phagocytes. These leukocytes consist of small cells which resemble lymphocytes, and larger cells known as macrophages. The macrophages contain clumps of pigment, red cells containing parasites, free parasites,

degenerated red cells, and even the small phagocytic cells which have been mentioned. The Malpighian bodies do not become pigmented but the fibrous trabeculæ always present marked pigmentation. The free pigment is present in the form of small rods or granules. Here, as in the liver, two forms of pigmentation occur, the dark brown or nearly black melanin, the malarial pigment, and the golden-yellow pigment, or hemosiderin, derived from degenerated red-blood corpuscles.

The *kidneys* in pernicious malaria present very marked lesions which have been studied especially by Ewing and Dock. The condition produced is generally an acute nephritis, presenting all its typical lesions with the peculiar lesions due to malarial infection. Microscopically the most marked change is the great congestion of the capillaries of the Malpighian tufts and the intertubular capillaries. These vessels are filled with infected red cells, free pigment, and pigmented leukocytes. There is also a marked pigmentation of the endothelial and epithelial cells, as well as those lining the tubules. Free parasites are often observed and may be seen occasionally within the glomerular capillaries. The epithelium of Bowman's capsule is undergoing marked proliferation and the capillary space may be entirely occluded. The epithelium of the tubules presents marked degenerative changes, consisting of fatty and albuminoid degeneration and necrosis. The straight tubules often contain hyaline, epithelial, or granular casts. There is not a marked pathological condition of the kidneys in every case, but it is safe to say that most cases of pernicious malaria are accompanied by an acute parenchymatous nephritis.

In certain cases the *bone-marrow* presents marked changes. Microscopically, unless the malarial infection has persisted for a long time, there is but little change. If weeks or months have elapsed, the color changes from the normal yellow to red or dull black. The capillary vessels contain numerous endocorpuscular parasites in various stages of development, and in estivo-autumnal infections, crescentic bodies. They also contain numerous macrophages, and in the marrow-pulp are found free parasites in various stages of development, as well as macrophages, nucleated red cells, and pigmented medullary cells.

All the changes described are not presented, as a rule, in every case. Some cases show marked changes in the spleen and liver, while the brain and kidneys are but slightly affected, and in others all the chief viscera show marked lesions. The pathology of *chronic* malarial infection or malarial cachexia, is characteristic. There is always a marked anemia, the spleen is greatly enlarged, sometimes weighing 10 or more pounds, and presents marked pigmentation. The liver is also enlarged but not in proportion to the size of the spleen. This organ also appears pigmented. The kidneys are enlarged and grayish in color, due to deposits of malarial pigment. This is also true of the brain cortex, and on section of the brain there is marked congestion of the capillaries, which contain numerous infected red cells, pigmented leukocytes, and free pigment. The condition is characterized by marked pigmentation of all the viscera, to which the name melanosis may well apply.

Pathology of Latent Malarial Infection.—By this term we mean cases in which no symptoms of malaria are presented, but in which death resulted from some other disease. During my service in the U. S. Army General Hospital, Presidio of San Francisco, 7 cases were observed in which the autopsy showed latent malarial infection; during life no symptoms of such infection had been presented. In 3 of these the infection was tertian and in 4, estivo-autumnal. The pathology of these cases is interesting as showing the lesions produced before the disease could be diagnosed. The pathological lesions were confined entirely to the spleen and liver. The spleen in the tertian infections was considerably enlarged and somewhat pigmented. The sections showed intense congestion of the sinuses with pigmentation, especially marked along the edges of the Malpighian bodies and the fibrous trabeculæ. Many of the cells of the splenic pulp were pigmented. In the splenic sinuses and in the capillaries there were numerous parasite-infected red cells and pigmented leukocytes, but such cells were not nearly as numerous as in acute infections. The parasites were characteristic of those in the peripheral blood and were all in about the same stage of development in each case. It happened that the patients died at such intervals that the entire human cycle of the tertian parasite could be worked out from an examination of sections of the spleen, and the chief point of importance in the pathology of latent infections, as observed in these cases, is that the entire human cycle of the parasite can be followed in the spleen when no parasites are demonstrable elsewhere, proving conclusively that the seat of the initial infection is in the spleen. The capillaries also contain numerous pigmented leukocytes and macrophages.

The *liver* in the tertian infections did not differ in appearance from the normal organ, but the capillaries showed within them a few pigmented leukocytes, some containing what appeared to be degenerated malaria organisms. No infected red cells were observed.

In the estivo-autumnal infections the lesions were the same and the life cycle of the parasite could be traced from the earliest hyaline organism to the segmenting bodies, but no crescents could be demonstrated. The only explanation of this is that the parasites had not advanced to the stage in which crescent formation was possible.

Symptoms.—Incubation.—There is considerable confusion regarding this. Marchiafava and Bignami found that the incubation period, from the time the patient was bitten by mosquitoes until the first symptoms appeared, varied from nine to ten days. From inoculation experiments, Bastianelli and Bignami found that in estivo-autumnal infections the maximum period of infection was five days, the minimum two, and the mean three days. Mannaberg in 7 cases found the period of incubation to vary from three to fourteen days, while Marchiafava and Bignami found the maximum to be fourteen days and the minimum two. As regards inoculation experiments, it may be stated that the disease was inoculated in an unnatural manner, and for this reason the data may be unreliable. In inoculation of blood containing only the forms of the parasite belonging to the human cycle it is reasonable to suppose that the period of incubation will be shorter than when the

mosquito transmits the *sporozoites* to man. This has been proved experimentally, for Marchiafava and Bignami found that in an individual bitten by a mosquito which had sucked blood containing crescents, estivo-autumnal fever developed in from nine to twelve days, whereas in the inoculation experiments of all the authorities quoted the mean was six days. But though the period of incubation is doubtless in the majority of cases from nine to twelve days, numerous instances occur which show a much longer period of incubation, sometimes weeks or months. The period of incubation may be very much prolonged, and in authentic instances personally observed the first symptoms of malaria did not appear until from seven to ten months after exposure. These were in officers and enlisted men of the army serving in a tropical climate, exposed to estivo-autumnal fever and who immediately afterward were stationed in localities in which there were no *Anopheles* mosquitoes and no endemic foci of malaria.

The explanation of these long periods of incubation is made clear by the theory advanced by Thayer, *i. e.*, that the parasites multiply and undergo their life cycle, but in such small numbers that they give rise to no observable clinical signs. Or it may be that latent forms are produced which remain inactive for long periods.

Although many individuals in malarial localities do not present symptoms of malaria for long periods, it is without doubt true that in the great majority of instances an individual exposed to infection will acquire the disease in from three weeks to two months. This was well illustrated in our soldiers in Cuba, almost 95 per cent. of whom gave a history of being there from two to six weeks before the onset of malarial fever. One month was the most common period intervening between landing in Cuba and the first chill.

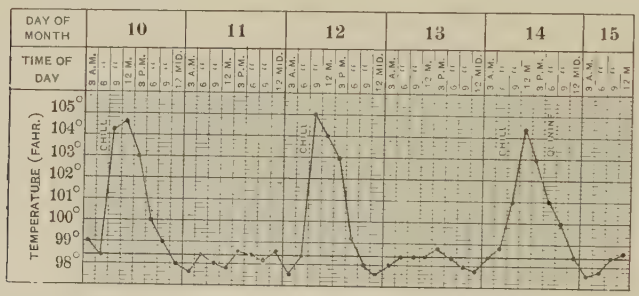
The length of the period of incubation will vary with the amount of the infecting agent, the physical condition of the infected individual and his surroundings as regards exposure, heat and cold, nourishment, etc.

Classification.—It is extremely difficult to classify the malarial fevers from a clinical standpoint. A division into intermittent, remittent, and continuous fevers, while useful, is at best but a rough classification which does not signify disease entities and is confusing in many ways. Any malarial fever may be intermittent, remittent, or continuous. For instance, while a single tertian infection is undoubtedly intermittent we can conceive of a tertian infection in which several generations of parasites mature at various times, causing a remittent or even continuous temperature curve. The same is true of quartan and especially of the estivo-autumnal infections. It is also true that infection with one generation of any of the malaria plasmodia will always result in an intermittent fever. In other words, *all* malarial infections are intermittent in character and only become remittent or continuous when more than one generation of the plasmodium matures at different intervals. While the term remittent malaria is generally applied to infections with the estivo-autumnal parasites, the name is a misnomer, as the estivo-autumnal infections are as truly intermittent as the tertian and quartan. For this reason it is better to classify the malarial fevers from an etiological standpoint, *i. e.*, tertian, quartan, and estivo-autumnal.

Symptoms of Tertian Malaria.—The paroxysms of fever in tertian malaria occur every forty-eight hours and are due to the segmentation of the tertian malaria plasmodium. The time of the paroxysm can be accurately judged by the stage of growth of the organism as seen in the peripheral blood. The onset of the paroxysm always occurs during the sporulation of the organism, and daily paroxysms are caused by double infections with the tertian parasite.

This, the most common and mildest form of malarial fever, occurs both in tropical and temperate climates, and when uncomplicated, presents a typical temperature curve, showing in single infections a rise of temperature every second day, while infections with numerous groups of tertian organisms may give rise to a remittent or subcontinued fever. In cases with daily paroxysms it is often possible to destroy one group of parasites by small doses of quinine, and, when this is done, the regular tertian paroxysm will reappear.

Fig. 46



Tertian malarial fever.

The paroxysm, when typical, is divided into three stages, chill, fever, and sweating. The *prodromal* symptoms are generally malaise, loss of appetite and more or less headache. After these symptoms have persisted for a few days the patient is seized with a severe chill, but although he feels extremely cold the temperature continues to rise and at the acme of the chill has reached 103°, 104°, or even 106° F. The chill is followed immediately by a pronounced sense of heat, and in a short time the patient complains as bitterly of this as he previously did of the cold. During the stage of fever, delirium is often present, accompanied by severe headache. At the onset of the chill, nausea and vomiting are common, but they do not persist, as a rule, during the stage of fever. After the fever has lasted for a few hours, it rapidly declines to normal, accompanied by very severe sweating.

The Cold Stage.—There are generally some prodromal symptoms of the approaching chill, evidenced by yawning, general malaise, headache, and often nausea and vomiting. The feeling of cold usually commences at the feet and gradually progresses upward, although very often the first chilly sensations are felt along the spine. In this form of infection the chill is severe, the patient shaking vigorously, but it is not so severe

as in the quartan infections. In certain mild cases the chill may be absent, the patient complaining only of chilly sensations. The facial expression shows cyanosis, the lips being blue and the skin bluish-red in color. The extremities are cyanotic and the skin presents the condition known as "goose flesh." The pulse is rapid, generally rather diminished in volume and often irregular. Headache is often intense. During the chill the temperature rises very rapidly, reaching 104° F. or more, but careful examination demonstrates that it has begun to rise before the onset of the chill. The urine is increased in quantity and lowered in specific gravity. The duration of this stage varies from fifteen minutes to two hours in the most severe cases.

The Hot Stage.—At the commencement of the hot stage the patient complains of flushings of heat, rapidly succeeded by cold sensations. Soon the sensations of cold are entirely lost and the patient complains of intense heat. The facial appearance shows congestion, the conjunctiva being injected and the skin red, while the entire surface of the body is reddened and the congestion is especially marked in the hands. The pulse is full, bounding, and often dicrotic. The respirations are often rapid and hurried, and there may be more or less cough, denoting congestion of the lungs. The headache increases and may become very intense and of a throbbing character. Epistaxis occurs in a small proportion of the cases. In the milder tertians there are no nervous symptoms beyond severe headache, but in the severe cases there may be marked delirium or a drowsy condition merging into a semicoma. This condition is almost always present in those rare cases of tertian infection which become pernicious. The chief complaints during the hot stage are severe headache and intense heat. The temperature may reach its extreme height during this stage but very often this is reached at the end of the cold stage. It is not uncommon during the hot stage to observe cutaneous eruptions. *Herpes* is very frequent, especially on the lips, and urticaria and a general erythema not infrequently occur. These eruptions sometimes lead to a suspicion of some eruptive disease being the cause of the chill. Herpes of the penis may occur. The duration of this stage varies somewhat, but is generally from four to six hours.

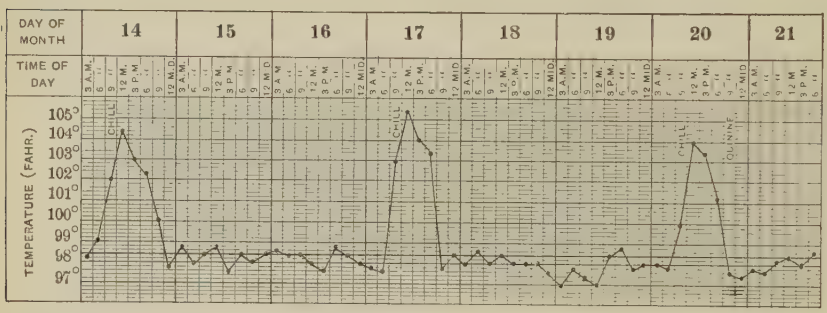
The Sweating Stage.—As the fever begins to decline, it will be noticed that perspiration appears first on the forehead and face, and the patient at once begins to feel better, the decrease in the unpleasant symptoms being proportionate to the severity of the sweating. Commencing on the face, the perspiration rapidly involves the entire body and is often so severe that water may trickle from the skin of the arms and legs. The sweating stage lasts, as a rule, from two to three hours, at the end of which time the temperature has reached normal, the unpleasant symptoms have disappeared, and the patient generally sleeps for some time. As a rule, the temperature goes below normal and the decline is accompanied by considerable weakness of the circulation. In very rare cases this stage may be accompanied by collapse, and in one case of pernicious tertian infection observed by the writer this collapse proved fatal. During the cold stage an excessive amount of urine is often voided, polyuria being frequent.

The average duration of the entire tertian paroxysm is from eleven to fourteen hours, but there are paroxysms so slight as to be hardly recognized, especially in children, while, on the other hand, the paroxysm may be prolonged to twenty-four hours. In children the onset is often accompanied by convulsions.

Examination generally shows an enlarged spleen, but this sign cannot be relied upon except in cases with severe and repeated infections. Albuminuria is present in a considerable proportion of the cases. Of over 1000 cases of tertian infection personally observed nearly 400 showed albuminuria, and 86 showed a few granular and epithelial casts.

Symptoms of Quartan Infections.—The quartan paroxysms occur every seventy-two hours, but here, again, we may have double infections in which the sporulation of the parasites occurs at irregular intervals, thus giving an irregular temperature curve. It is not necessary to detail the symptoms as they differ in no way from those in tertian infections except that, as a rule, they are more severe and these infections are more

FIG. 47



Quartan malarial fever.

apt to become pernicious. There are the same stages of chill, fever, and sweating as in the tertian infection. The nervous symptoms are very much more pronounced, the headache being more severe, and slight delirium being almost always present. The quartan paroxysm is not as prolonged as the tertian, seldom covers more than ten hours, and is due to the sporulation of the quartan parasites.

Symptoms of Estivo-autumnal Infections.—Clinically, all estivo-autumnal infections should be classed as severe infections, in contradistinction to the quartan and tertian infections, which are usually considered as mild infections. It should be understood, however, that a quartan or tertian infection may become pernicious, although such instances are rare. The old idea that there is a malaria parasite peculiar to the pernicious infections is not tenable, for it is recognized that any of the malaria parasites may induce pernicious symptoms, and that the parasites accompanying such infections do not differ in any respect from those accompanying the mildest infections.

The estivo-autumnal infections occur in temperate regions most fre-

quently during July, August, September, and October, but in the tropics they persist throughout the year, and are not always characterized by any marked seasonal prevalence.

The writer believes that these infections are caused by two distinct varieties of the estivo-autumnal parasite, one completing its cycle of development in the human body in twenty-four hours, and the other in forty-eight hours. Either of these parasites is capable of causing pernicious infections, but personal observations suggest that the tertian estivo-autumnal parasite is the one most commonly concerned. From personal observations embracing nearly 2000 cases of estivo-autumnal fever in which the parasites were demonstrated in the blood, 88 per cent. were due to the tertian estivo-autumnal variety.

The estivo-autumnal infections have long been distinguished by the term remittent, it being supposed that in these infections the temperature curve, instead of presenting the marked intermittency of tertian and quartan infections, was remittent or irregular. This is not always correct, for these infections, when uncomplicated or uninfluenced in any way by treatment, may be as truly intermittent as the tertian and quartan infections. It is undeniable, however, that remittency and irregularities in the temperature curve are more common in estivo-autumnal infections, but too much stress should not be laid upon this point in diagnosis.

Symptoms of Tertian Estivo-autumnal Fever.—*Prodromal.*—The prodromal symptoms are loss of appetite, slight headache, evanescent pains in the back and legs, nervousness, increased urination, and a general feeling of malaise.

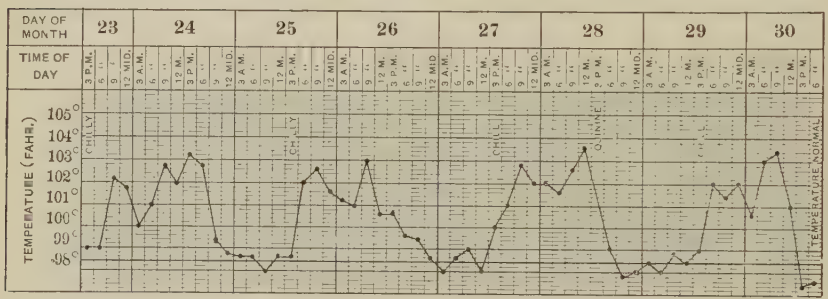
The Cold Stage.—This commences with yawning and the patient complains of headache, slight nausea, perhaps accompanied with vomiting, and often intense nervousness. In a majority of cases there are no distinct chills, but the patient complains of creeping sensations along the spine, and slight feelings of cold especially noticeable along the posterior portion of the buttocks and thighs. At the same time the headache increases and there is generally profound mental depression. The mucous membranes are cyanosed and the extremities cold. There is severe pain in the legs and back, greatest, as a rule, in the lumbar region. The pulse is generally weak and increased in frequency and may be very irregular. The respirations are rapid and rather shallow. During this stage the temperature is elevated and may reach 103° F. or more. This stage does not last over one-half hour in a majority of the cases.

Hot Stage.—The patient next experiences a sense of heat which comes first as localized flushings, but soon becomes general. The facial expression shows the eyes suffused and brilliant, the face red, and the skin hot and dry. Headache is intense and there is either great mental depression or nervous excitement. The pain in the back and limbs is often agonizing and in some instances there is severe pain over the abdomen. The temperature is elevated and the curve very characteristic. Nausea and vomiting are often present, vomiting being sometimes very severe. The urine is increased in quantity and generally albuminous. Diarrhœa is a common complication. The pulse is rapid and dicrotic, the respiration rapid, and there may be severe dyspnœa. This stage lasts for several

hours, often from sixteen to eighteen or twenty, and is succeeded by a stage of remission. During this time the symptoms gradually decline in severity and finally disappear, the temperature returns to normal, generally going a degree or degree and a half below normal. A slight sweating occurs, but this is not nearly so marked as in the tertian and quartan paroxysms. The intermission may last only two or three hours when another paroxysm ensues. As a rule, attacks of this fever occur toward evening, extend throughout the next day, and subside during the first hours of the third day, the entire paroxysm thus lasting thirty-six hours or more and occurring every forty-eight hours.

While the symptoms described are often more severe than in the tertian and quartan infections, there is nothing diagnostic about them except the temperature curve. In uncomplicated cases the behavior of the temperature is absolutely characteristic, and the curve is one not met with in any other disease. This peculiarity of tertian estivo-autumnal infection was first pointed out by Marchiafava and Bignami, and the writer has confirmed their observations in every uncomplicated case of

FIG. 48



Tertian estivo-autumnal fever.

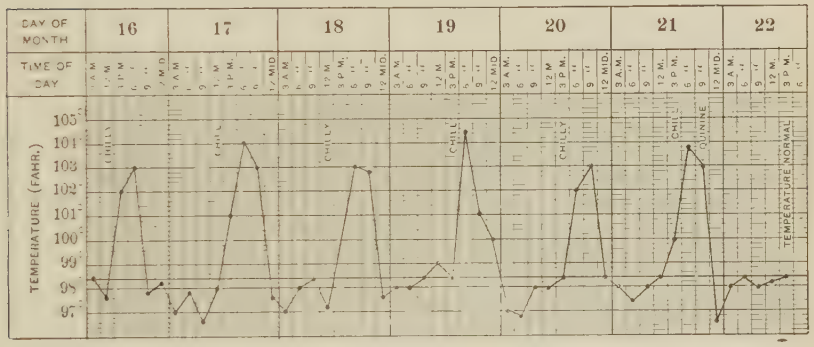
such infection. At the onset of the fever the temperature rises suddenly to 103° or 104° F. Following the sudden rise there occurs slight oscillation which covers several hours, during which time the temperature falls from $\frac{1}{2}$° to 1°. This period of oscillation is followed by a distinct fall or pseudocrisis, the temperature dropping from $1\frac{1}{2}$° to 2°, or even 3°, which is often regarded as the true crisis of the paroxysm, but the fever again rises to a point higher than before and then falls rapidly. This is the true crisis, as the temperature goes below normal. This temperature curve can be divided into five stages: (1) The initial rise; (2) the period of slight remissions; (3) the pseudocrisis; (4) the precritical stage; (5) the true crisis.

Another point of value in diagnosis between this type of fever and the mild tertian and quartan types is the duration of the fever. This varies, but generally the temperature remains elevated over twenty-four hours, and often from thirty-eight to forty; the paroxysm really covers two days, while the period of intermission is very short. While this peculiar temperature curve is observed in a very large proportion of cases of tertian

estivo-autumnal malaria, there may be many deviations from it due to several factors, among the most important being improper medication, double infections, or infection with more than one variety of malaria parasite; anticipation of the attacks or retardation, especially common in the pernicious forms; and slight elevations of temperature between the paroxysms. The ordinary temperature chart which shows only the morning and evening temperature is worse than useless as a guide in studying this form of fever. The temperature should be taken at least every four hours and better every three.

Symptoms of Quotidian Estivo-autumnal Infections.—The rare quotidian infection, due to the quotidian form of the estivo-autumnal parasite, varies but slightly in its symptomatology from the tertian, except that the paroxysms occur every twenty-four hours. As a rule, in the quotidian cases the chilly sensations are more severe and there is often a distinct chill. Sweating is also more pronounced but is not so marked as in the

FIG. 49



Quotidian estivo-autumnal fever.

simple tertian and quartan fevers. The temperature curve is entirely different. It shows an abrupt rise to 103° F. or more, succeeded by as abrupt a fall. The attack lasts as a rule only about eight or ten hours. The temperature curve seldom remains regular for long at a time, for the attacks tend to run into one another, giving rise to a continuous fever. This is especially true in cases of a pernicious type. The temperature curve in the quotidian form is not characteristic as it resembles closely that of double tertian infection.

Pernicious Malarial Infections.—Any one of the malaria plasmodia may give rise to pernicious symptoms, but the vast majority of fatal cases of malarial fever are due to the estivo-autumnal parasites. The tertian estivo-autumnal parasite is more often concerned in such infections than the quotidian, but tertian infections are very much more numerous than quotidian. It is very important in treating cases of estivo-autumnal malaria to remember that there is always an element of danger in that they may at any time develop pernicious symptoms which may

cause death, and that the pernicious forms depend for their etiology upon the same organisms as do the mildest forms.

The great majority of pernicious attacks of malaria in northern latitudes occur in the summer and autumn and are rare, while in the tropics they occur throughout the year and are very common. The most pernicious attacks occur in patients who have suffered repeatedly from malaria paroxysms which have not been properly treated, and the pernicious symptoms often develop during such a paroxysm. The causes of the pernicious symptoms are not very clearly understood. Bastianelli and Bignami considered that the chief causes rest in the localization of the parasites in the brain or in other important organs, and also in the number of parasites present. While these undoubtedly have much to do with the development of pernicious symptoms, it is probable that the amount of toxins secreted by the parasites have much to do with the development of these symptoms, as well as the physical condition of the patient and his surroundings as regards climate, food, hardships, etc.

The pernicious forms of malaria may be classified either from the character of the temperature curve or from the most prominent symptoms. Under the first classification we may have *tertian, quartan, remittent,* or *larval* pernicious malaria. Under the second we may have *comatose, delirious, tetanic, eclamptic, hemiplegic, dysenteric, choleraic, algid, cardialgic, hemorrhagic, pneumonic,* and *bilious* pernicious malaria fevers. Only a few of the most common varieties will be described; these are not disease entities but take their names from the clinical symptoms.

The Comatose Form.—This is the most frequent form of pernicious malarial fever and occurs either as a sudden attack of coma or a gradually developing comatose condition during a paroxysm of fever. The sudden development of coma is rare and, unless at once recognized and treated, invariably fatal. In this form the patient, who may have suffered from repeated attacks of malaria and who has not felt well for some time, is suddenly stricken with profound coma, falls to the ground, and, in fatal cases, does not regain consciousness. This form is apt to be mistaken for apoplexy. The face is suffused, the pupils contracted, the pulse at first full and bounding, later soft, rapid, and thready, the respirations hurried and sometimes stertorous. The temperature is irregular, seldom reaching 103° F., and is often subnormal. Death generally occurs within two days. The most common form is that in which coma develops more or less gradually during an attack of the fever. The symptomatology of the attack is the same as in the ordinary paroxysm, but the nervous symptoms such as restlessness and delirium may be more marked. As a rule, the patient is restless and mentally depressed. Following this there is a tendency to somnolence, which deepens into stupor and finally coma. Unconsciousness is complete, the patient lying perfectly quiet, or there may be restless movements of the arms and legs. The skin is often somewhat icteric, and hot and dry; the pupils are generally equally contracted, but may be unequal or equally dilated. The icteric hue, often present in the conjunctivæ, has led to a diagnosis of yellow fever in infected regions. The face may be cyanotic but in old infections it is generally pale. Slight spasms of the muscles of the face are not infrequent. The

tongue is tremulous, dry, and thickly coated, and slight hemorrhages into the skin are sometimes observed. There may be hemiplegia or total paralysis. The respirations are slow and quiet, but may be irregular, rapid, and stertorous. The pulse is generally slow, full and incompressible at first, but becomes rapid and weak as the paroxysm progresses. The feces and urine are passed involuntarily and retention of urine may occur. In cases having a fatal termination the pulse becomes thready, rapid, and intermittent; the respirations irregular, labored, or shallow; the skin pale and bedewed with cold perspiration, and death occurs by collapse. In patients who recover, the temperature falls, accompanied by perspiration, the consciousness is slowly regained, but in many of these cases the improvement is only apparent and the patient relapses in a few hours into a second paroxysm, and perhaps into a third, which usually results fatally. Between the paroxysms the mental condition is of torpor or great mental depression accompanied by severe headache. The duration of the coma is variable, lasting from a few hours to three or four days, but it generally does not persist longer than twenty-four to twenty-six hours.

The temperature in this form is irregular. Some present high fever throughout, between 103° and 104° F., while in others the temperature remains slightly above normal or subnormal. In fatal cases the fever if present, declines, as a rule, before death, but it may ascend. Manson cites temperatures of 101° and 112° F. In a fatal case observed by the writer the temperature never went above 101° F. until a few hours before death, when it rose to 103°, the entire attack lasting six days.

Besides the comatose form there are other cerebral forms, among which are the *delirious* form in which the patient has hallucinations, followed by violent excitement; the *eclamptic* form, common in children, in which the symptoms are similar to those of cerebrospinal meningitis, with vomiting, fever, headache, pain in the back of the neck, convulsions, and coma; the *hemiplegic* form; and the *amaurotic* form, in which complete blindness may result.

The Algid Form.—In certain regions of the Southern and Middle States, as well as in other localities, there occur pernicious forms of malaria known as algid forms. The symptoms develop after one or more paroxysms, or they may be the primary symptoms. The characteristic condition is one of profound collapse with profuse perspiration, the temperature at the same time being more or less elevated, although in many cases it is subnormal. Patients with this form of malarial infection present a characteristic countenance, the cheeks drawn and pinched, the eyes sunken, the nostrils dilated, and the skin bedewed with perspiration. The entire body is cold and the skin cyanotic and bathed with cold sweat. The lips and finger nails are intensely cyanotic. The tongue is tremulous, dry, and coated with a dirty white fur. The pulse is rapid, thready, and easily compressible, and generally more or less intermittent; the heart-sounds are muffled and the second sound sometimes inaudible, and as death approaches the pulse becomes imperceptible; the respirations are irregular, superficial and labored; the muscular weakness is extreme, while the mental condition is one of apathy and

indifference. These symptoms rarely last over a few hours, death generally resulting. This is one of the most pernicious types of malarial infection and most resistant to treatment.

The Choleraic Form.—The patient may present symptoms which closely simulate those of cholera. Diarrhœa is not infrequent in estivo-autumnal fever, but in these cases choleraic symptoms develop, the stools suddenly becoming watery, very profuse and numerous. The diarrhœa leads to profound collapse. Death is a common result in untreated cases, but when therapeutic measures are applied promptly, recovery occurs in the majority. The temperature is generally elevated. The great importance of this variety consists in danger of mistaking it for cholera in countries in which cholera occurs.

Closely allied, so far as symptoms pointing to the abdomen are concerned, is the *gastralgic* form which has been described by Laveran, Colin, and Haspel. Prominent features are agonizing pain in the epigastrium, the vomiting of matter tinged with blood, and a severe diarrhœa may occur at the same time. This form is interesting from a surgical standpoint, as a diagnosis of appendicitis may be made.

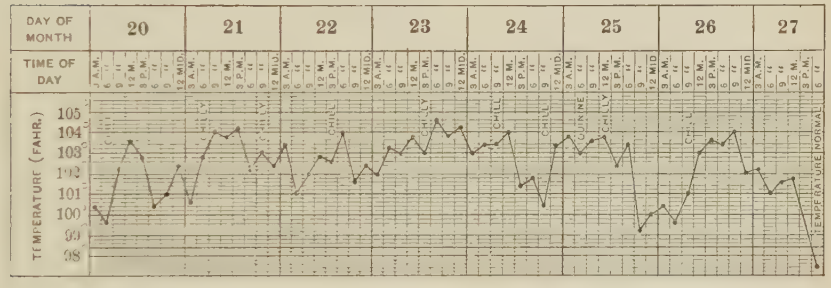
The Dysenteric Form.—A considerable proportion of patients suffering from estivo-autumnal infection present symptoms of dysentery, consisting in frequent mucoid and bloody stools, tenesmus, colicky pain in the abdomen, progressive emaciation, etc. Dysenteric symptoms in the tropics are often due to malarial infection.

The Bilious Form.—Certain cases present a symptom complex in which jaundice and the vomiting of bile-stained fluid are most prominent. These cases have long been known under the term of "bilious remittent fever." The attack is generally characterized in the beginning by well-marked malarial paroxysms, but the temperature becomes more or less remittent or continuous. Marked jaundice appears and severe vomiting is present, the matter vomited being greatly bile-stained. Epistaxis is rather common and hematemesis often occurs. Delirium, semicoma, or even coma may be present. The patient often complains of severe pain in the epigastrium, and hiccough is common. The temperature curve in well-marked cases is generally remittent or almost continuous, somewhat resembling that of typhoid fever. If untreated, this form is almost invariably fatal, but if proper therapeutic measures are applied recovery generally results.

Irregular and Remittent Forms.—Any malarial infection may become irregular or remittent as regards the temperature, but the estivo-autumnal infections especially present irregularities in the fever, which in many cases are very confusing. A malarial fever may become continuous, irregular or remittent in various ways, the principal of which are the anticipation or retardation of the paroxysm, infection with one or more groups of parasites, and insufficient treatment by quinine. In these infections it is very seldom possible to demonstrate the complete life cycle of the parasite in the blood, but in those cases caused by mixed infection with more than one variety of parasite the forms may be easily differentiated. It is these forms, especially the remittent or continuous types which are so often confused with typhoid fever and septicemia, especially where estivo-autumnal infections are infrequent.

The *remittent* type is of the most importance, as cases of this kind are not infrequently supposed to be typhoidal. The features are very variable and inconstant. The prodromal symptoms are generally weakness, malaise, headache, loss of appetite, etc. The attack may or may not begin with chills but there are always slight chilly sensations. The patient's appearance is suggestive of typhoid, the face being flushed, the eyes brilliant, the mucous membranes congested, and the skin hot and dry. There is severe headache and muscular pain, especially in the back and limbs. There is often marked nervousness, sleep being poor, and there may be slight delirium. The tongue is dry and coated, while nausea and vomiting are present and diarrhœa is common. The pulse is rapid and dicrotic, while the respirations are hurried and often very superficial. There is often tenderness of the abdomen, and the spleen is generally enlarged. In some cases the resemblance to typhoid is very remarkable, epistaxis, an eruption resembling the roseola of that disease, and tenderness and gurgling in the right iliac region being present. The

Fig. 50



Subcontinued estivo-autumnal malarial fever.

temperature curve in these infections is very variable, but usually there are more or less marked intermissions. In rare cases the curve cannot be distinguished from that of typhoid fever, there being slight daily remissions but no marked intermissions.

An examination of the blood, if carefully made, will invariably demonstrate the malaria parasite concerned, which is generally one of the estivo-autumnal organisms. If properly treated, the symptoms are controlled within a week, although in very rare instances the parasites may be very resistant to quinine and persist for eight to ten days.

Combined Infections.—Any of the varieties of malaria plasmodia may occur together, causing what is known as a combined infection. In such infections the temperature chart is apt to be irregular or remittent, but one type of parasite may so predominate that it gives to the infection its characteristic symptoms; thus we may have a combined infection with estivo-autumnal and tertian parasites in which the former are so much more numerous that the case presents the symptoms of an estivo-autumnal infection.

Latent and Masked Infections.—The writer has called attention[1] to the importance of latent and masked malarial infections, especially in individuals who have resided in malarious localities. A *latent* malarial infection is one in which parasites can be demonstrated in the blood but in which there are no symptoms which would lead a clinician to suspect malaria, while a *masked* infection is one in which the symptoms are obscured by those of some accompanying disease, or in which they are atypical in character. At the U. S. Army General Hospital in San Francisco, of 1267 cases of malaria in which parasites were demonstrated in the blood, 395, or 25 per cent., showed either latent or masked infections. The estivo-autumnal infections comprised 275 of the cases, showing that this parasite is concerned most often in latent and masked malaria. Examinations of the blood in such cases have shown the parasites in all stages of development, but always in small numbers. Of the 395 cases, 277 were latent infections, or infections in which the malaria parasites could be demonstrated in the blood but which presented no clinical symptoms, while 118 were masked infections, the majority in patients suffering from other diseases which masked the malarial symptoms. Of the masked infections, chronic dysentery, chronic diarrhœa, pulmonary tuberculosis, and amœbic dysentery most often masked the malarial infection. Lobar pneumonia was simulated very closely in 3 cases by the malarial infection.

This remarkable percentage of latent and masked infections proves the great importance of a routine examination of the blood in all patients from malarious localities. Recognition of such infection is of the greatest importance, as in the latent infections we are able to cure the disease before any annoying symptoms are present, and in the masked cases we are able to remove the malarial element which may be of great importance as regards recovery. An examination of the blood in these cases will often prove of service, not only to the physician, but also to the surgeon, as certain malarial infections simulate surgical conditions, especially appendicitis, very closely.

Complications.—The conditions complicating malarial infection should not be confused with the infection itself; typhoid fever complicating malaria should not be considered as being due to malarial infection; nor is a complicating pneumonia necessarily due to the malarial parasites. Of the diseases which may complicate malaria, especially the estivo-autumnal infections, the following may be mentioned:

Of the diseases of the *nervous* system, acute mania, severe hysteria, paraplegia, hemiplegia, and meningitis may be noted.

The most serious diseases of the *respiratory* system complicating malarial infections are lobar and bronchopneumonia. For a long time pneumonia complicating these fevers was held to be due to the malaria plasmodia, and while this is true in a very small number of cases, true pneumonia may occur coincidently with any of the malarial fevers. Pneumonia may complicate the malarial infection at any time, and may develop suddenly or insidiously. The course of the disease is similar

[1] *Med. Rec.*, February 15, 1902, also *Am. Med.*, October 21, 1904. *The Malarial Fevers, Hemoglobinuric Fever, and the Blood Protozoa of Man*, New York, 1909, p. 228.

to that in a patient in whom no malarial infection is present, but the prognosis in pneumonia complicating the estivo-autumnal infections is very grave, Ascoli placing the mortality as high as 60 to 78 per cent. The pneumonic symptoms may mask the malaria, or *vice versa*. Acute bronchitis is common in all varieties of malarial infection and in the estivo-autumnal forms occurs in about 40 per cent. of the cases. Tuberculosis often occurs with malarial infections, and often the symptoms of this disease mask those of malaria. Pleurisy is somewhat rare.

Diseases of the *circulatory* system not infrequently complicate malarial fevers. Many cases of malaria present organic disease of the heart and in such cases the prognosis is often grave. Acute endocarditis is rare while functional disorders of the heart are very common.

The most common disease of the *genito-urinary* system complicating malaria is nephritis. It is more frequently a sequel than a complication. Orchitis and epididymitis very commonly occur as complications, but a history of gonorrhœa can usually be obtained. It is doubtful if true malarial orchitis ever occurs.

The most frequent and important disease of the *gastro-intestinal* tract complicating the malarial fevers is dysentery or some form of enteritis. Dysentery is especially frequent in patients returning from regions where both malaria and dysentery are endemic. Dysentery complicating malaria is very apt to run an aggravated course, and the prognosis is much worse than when it occurs alone.

The administration of quinine in cases complicated by dysentery has always resulted in the removal of the malarial infection and improvement of the dysentery. In a certain proportion of patients with dysentery, the disease is probably due to the localization of the malaria parasites in the capillaries of the intestines, for in no other way can we explain the rapid recovery of many such patients after giving quinine.

Typhoid fever occasionally occurs with the malarial fevers. In nearly 5000 cases of malaria personally observed this association has occurred only 10 times. Of these 10 cases, 6 were combined infections of typhoid and estivo-autumnal malaria, 3 with tertian malaria, and 1 with quartan. As a rule, the malarial attack occurs during convalescence from typhoid fever but may occur during any stage of the disease. When malaria is complicated by typhoid, or *vice versa*, the symptoms do not vary markedly from those occurring in a single infection.

The discovery of such combined infections is of great importance, as the malarial element can be removed by giving quinine.

Among other complications may be mentioned erysipelas, rheumatic fever, sciatica, various skin eruptions, and variola.

Sequelæ.—The most common are those occurring in the *nervous* system, the *genito-urinary* system, the *glandular* system, and the *blood*.

The most numerous complications occur in the *nervous system*, due to blocking of the capillaries of the cortex of the brain by malarial parasites and their products, or to the effect of toxins liberated by them. Local paralysis frequently occurs, due undoubtedly to blocking of the capillaries of certain cortical regions, but these are generally evanescent. Various psychical disturbances are common and the memory is often defective

after repeated malarial attacks. Melancholia, delusional insanity, and mania may follow severe attacks of estivo-autumnal malaria, and especialy common is a condition of melancholia. Mania, melancholia, and delusional insanity have been observed in soldiers returning from the tropics which were undoubtedly sequelæ of severe and repeated attacks of estivo-autumnal malaria. Multiple neuritis rarely occurs. A common sequel is neuralgia, but many so-called malarial neuralgias have no connection whatever with malarial infection.

In the *genito-urinary* system, albuminuria is frequent during acute attacks of malaria and often persists for some time after the cessation of such attacks. Thayer found that albuminuria was most frequent in estivo-autumnal infections, occurring in 58.3 per cent. of these, in contrast to 38.6 per cent. of tertian and quartan infections. From personal experience, albuminuria apparently occurs in about 65 per cent. of cases of estivo-autumnal and in about 30 to 35 per cent. of cases of tertian and quartan malaria.

Both acute and chronic *nephritis* may occur as sequelæ. All forms may occur, the most common being acute glomerular and chronic parenchymatous and interstitial nephritis. Personal observations suggest that nephritis occurs in at least 4 per cent. of all cases of estivo-autumnal infections, the most common form being chronic parenchymatous. It is rare in tertian and quartan infections, but is always found in fatal cases. *Polyuria* is a frequent sequel of the malarial fevers, especially the estivo-autumnal variety, but, as a rule, the condition is transient, although it may be persistent. *Glycosuria* is a rare sequel.

Among the sequelæ in the *glandular* system are hypertrophy of the liver and rupture of the spleen. After repeated attacks of malaria, a condition which may be termed hypertrophic, malarial hepatitis, may develop, the liver becoming greatly enlarged, while the perilobular tissue is increased in amount and the capillaries greatly dilated and congested. The condition does not, as a rule, cause any clinical symptoms. Many authorities have endeavored to prove that continued malarial infection gives rise to cirrhosis of the liver, but when present it is undoubtedly due to some other cause, as cirrhosis of the liver is no more common in malarial than in non-malarial districts.

Rupture of the spleen is a rare sequel of malaria and is generally due to falls or blows, by which the greatly enlarged organ, rendered soft and pliable by the malarial infection, is ruptured. The writer has reported 2 cases of this character. The symptoms are sharp, lancinating pain in the left side and the usual symptoms of collapse due to hemorrhage. Death may occur in a few moments or after a day or more.

The Blood.—In repeated and severe attacks of estivo-autumnal malaria an anemia is produced which may be very severe and persistent. In tertian and quartan infections, after complete recovery, the regeneration of the red-blood corpuscles is generally rapid, but in the estivo-autumnal infections the anemia may persist. There is a marked reduction in the hemoglobin, always in about the same ratio as the red cells, while the leukocytes are reduced in number as a whole, but the large mononuclear forms increased.

A pernicious type of anemia, as a sequel of the estivo-autumnal infections, has been observed by the writer in 6 cases, all of which proved fatal. The blood showed no nucleated red cells, the red cells numbering from 490,000 to 590,000 per c.mm. The leukocytes were about normal in number, relatively, but the polymorphonuclear leukocytes were increased. Poikilocytosis was not marked, but there were great differences in the size of the red cells. This form of severe anemia is remarkable in that no nucleated red cells can be demonstrated, due, perhaps, to the almost complete absence of regenerative power in the blood-forming organs. In some instance the classical type of pernicious anemia occurs as a sequel especially of the estivo-autumnal variety.

Malarial Cachexia.—In patients who have suffered from repeated attacks of malarial fever which have not been properly treated, a peculiar condition develops, the most characteristic features of which are a more or less severe anemia and a greatly enlarged spleen. This is most frequent in tropical regions in which the estivo-autumnal infections are endemic, and least frequent in localities in which tertian infections are present. It is especially apt to develop after untreated latent and masked infections. The anemia has the characters of a secondary anemia, the red cells being reduced to 2,000,000 or less per c.mm. while there is a marked increase in the large mononuclear leukocytes and a corresponding decrease in the hemoglobin. The spleen may be enormously enlarged, reaching as low as the crest of the ilium, but it usually does not extend more than 4 to 8 cm. below the border of the ribs. It is firm and not painful on palpation.

Patients suffering from malarial cachexia present a peculiar yellowish or grayish hue of the skin, while the mucous membranes are very pale. There is a loss of appetite, diarrhœa, dyspnœa, emaciation, and general nervous exhaustion. The temperature may be normal, but generally shows a slight rise toward evening; it seldom reaches 102° F. The condition is especially frequent in children living in tropical localities.

The long-continued malarial infection renders these patients especially liable to acute infectious diseases, and slight injuries are often attended by serious results, such as phlegmonous inflammation or hemorrhage. Marchiafava and Bignami state that it has never been their experience to observe in patients suffering from malarial cachexia, grave infections with many parasites in the blood, but that there are always a few parasites and very little melanemia. Malarial cachexia cannot always be determined by microscopic examination of the blood, as the parasites will not be present in any number except when there are acute symptoms, and even melanemia may be almost absent.

Latency and Recurrence.—Examinations of the blood of persons residing in malarial localities often show the presence of the parasites although no symptoms are present. In such instances the infection is said to be *latent*. It is also well known that most patients with malaria improperly treated relapse sooner or later, and during the period between the relapses the disease is also latent. Of 1297 cases of malaria in Americans returning from the Philippines studied by the writer, no less than 307, or nearly 24 per cent., were latent infections, and in the Philippines of 225 Filipinos, apparently in good health, 115, or 51 per cent., showed a latent malarial

infection. The subject of *recurrence* is of great importance and much work has been done upon its etiology. If physicians properly treated their malarial patients recurrences would be comparatively rare, and the danger of patients becoming malarial carriers would be practically obviated. Recurrences are undoubtedly due to a certain number of plasmodia escaping the effects of quinine, and living in some form in the body until conditions are favorable for their multiplication, when a relapse results. The time of recurrence varies in the different infections. In 55 cases of tertian estivo-autumnal infection observed personally the time of recurrence varied from ten to eighty days; the greatest number of relapses occurred between the twentieth and thirtieth days, namely, 23, and almost as many between the thirtieth and fortieth days, namely, 16. In most instances secondary relapses occurred at longer intervals than the primary relapse. Of 18 tertian cases in which relapse occurred, the shortest period of relapse was sixteen days, and the longest was forty-one days; most of the cases relapsed between the fifteenth and thirtieth days.

The following table compiled from the observations of others and the writer gives a composite picture of the incidence of latent malaria in most localities where these infections are endemic. This table gives the number and percentage of latent malarial infections, at various ages, as ascertained by the finding of the plasmodia in the blood of the individuals examined.

PREVALENCE OF LATENT MALARIAL INFECTION AT VARIOUS AGES

Age.	Number examined.	Number infected.	Per cent.
1 to 5 years	6,288	1407	22.3
5 to 10 years	5,305	1279	24.1
10 to 15 years	3,480	966	27.7
Adults	15,440	3164	20.4
Totals	30,513	6816	20.4

The exact cause of latency and recurrence is still unknown. There are three theories suggested. The theory of Ross is that the plasmodia are always present and undergo their normal schizogony, but in such small numbers that no symptoms are produced during the period of latency, and that relapse is due to rapid multiplication brought about by favorable conditions. The theory of Schaudinn is that relapse is due to parthenogenesis of the *macrogamete*. The theory of the writer is that latency is produced by the intracorpuscular conjugation of the young *schizonts*, leading to the production of a resting form, which, when conditions are favorable, undergoes multiplication, and a relapse occurs. There is evidence in favor of all these theories, but no one of them can be said to be scientifically proved. It is quite probable that the theory of Ross is correct as regards short-term relapses, but it is reasonable to believe that some resting form of the plasmodia must exist to explain relapses after several months, the so-called "long-term" relapses. Bignami believes that relapses are due to the sporulation of quinine-fast strains of malaria plasmodia, but there is little, if any, evidence of the existence of such strains, despite an immense amount of work done in

the endeavor to prove that quinine-fast strains of the malaria plasmodia can be produced experimentally by long-continued treatment with small doses of the drug.

Diagnosis.—From clinical symptoms alone this is often difficult and sometimes impossible, especially in the estivo-autumnal infections, but two methods are all-sufficient and deserving of confidence, *i. e.*, examination of the blood and the therapeutic test by quinine. Of these two methods the examination of the blood is the more valuable, for the therapeutic test may be misleading. The mild tertian and quartan infections, if uncomplicated, can usually be easily diagnosed by clinical symptoms alone, but when double infections occur, a diagnosis of malaria is often impossible from a clinical study, and in estivo-autumnal infections a diagnosis of malaria is generally impossible without an examination of the blood.

Examination of the Blood.—In most instances one examination is sufficient, but with a negative result repeated examinations should be made at short intervals. If this is done, almost invariably, even in the most obscure estivo-autumnal infections, the parasites will be discovered. Cases of malaria of this variety undoubtedly occur in which no parasites can be demonstrated in the peripheral blood, but not when the infection is severe enough to produce symptoms. The symptoms in estivo-autumnal infections are often so obscure, or even so slight, that malaria is not suspected, and in many cases an examination of the blood will show the presence of the malaria plasmodia before any clinical symptoms appear sufficiently severe to excite a suspicion that the infection exists. An examination of the blood in all cases of disease in malarious localities should be a routine measure.

The blood may be examined either in the fresh state or in stained specimens. The desirability of the examination in the fresh condition rather than in permanent specimens, which have been fixed and stained, has been advised, but since the development of Wright's modification of Romanowsky's stain, the examination of specimens stained by this method is preferable, except in the hand of an expert, to the examination of the fresh blood. For the examination of certain stages in the life cycle of the plasmodia, the examination of fresh blood is essential, but with improved methods of staining, better results will be obtained by the majority of physicians if stained specimens are used.

Examination of Stained Specimens.—There have been numerous methods proposed for the staining of the malaria plasmodia, the most valuable of which have been Romanowsky's and its many modifications, such as Jenner's and Wright's. Probably the most satisfactory is the modification of Romanowsky's stain described by Wright. While the method of preparing the staining solution is somewhat complicated, a careful following of the directions will result satisfactorily. Dr. H. R. Oliver modified Wright's method slightly, and the staining solution as prepared by him gives excellent results. The following is the method of preparation:

Wright's Stain.—In a flask add 0.5 gm. of S. P. bicarbonate of soda to 100 cc. of distilled water, dissolve thoroughly, and slowly add, while

shaking, 1 gm. of methylene blue; heat for one hour in an Arnold sterilizer after the steam is up and then cool the solution. Make a solution of yellow aqueous eosin by adding 1 gm. of the eosin to 1000 cc. of distilled water, and add this, while stirring, to the cooled methylene blue solution until a well-marked precipitate appears and the surface of the mixture is covered with a greenish metallic scum. Test by placing a drop of the mixture upon filter paper; when sufficient eosin solution has been added a well-marked pink halo should surround the small amount of violet precipitate upon the paper. Allow the mixture to stand for about ten minutes and then filter through one small filter paper; after filtration is complete remove the paper from the filter, unfold it so that it is half folded, and press between several thicknesses of blotting paper; remove the upper half of the paper, when all of the precipitate will be found upon the lower half. The precipitate is carefully removed, placed in a glass dish, and dried in a hot-air oven at 60° C.; it is then crushed into a powder which is used in preparing the staining solution as follows:

Take 0.3 gm. of the powder and dissolve it in 100 cc. of methylic alcohol (Merck's reagent), filter, and bring the filtrate up to the original 100 cc. by adding the requisite amount of methylic alcohol. The staining solution is now ready for use and will keep well for months.

Method of Using.—Add a few drops of the staining solution to the blood smear and let stand for from three to five minutes; this fixes the specimen. Then add enough distilled water to the preparation to cause a metallic scum to appear upon the surface; let stand for from three to five minutes; wash in distilled water; examine directly when dry or mount in neutral balsam. The washing with distilled water is important, as it removes the precipitate generally formed during the staining process, and differentiates the chromatin of the nucleus of the parasites.

By this method all varieties of malaria parasites stain as follows: The protoplasm stains a robin's-egg blue, the vesicular portion of the nucleus remains unstained, while the chromatin stains a dark cherry-red. The very young forms of the plasmodia—that is, the ring forms—are very distinctive, appearing as a bright blue ring, at some portion of which is situated a dark cherry-red dot marking the chromatin of the nucleus, the red cell being stained a light red or brownish-yellow.

The only objection to the use of staining methods is that certain other material, especially broken-down leukocytes or extraneous matter, may take the stain and be so situated within the red cells as to be mistaken for the plasmodia. But to one who has studied preparations stained by the method described, no such mistake is possible.

Differentiation in Stained Preparations.—The malaria plasmodia may be easily differentiated in stained preparations. The following points are useful in differentiating the various species:

Plasmodium vivax.—(Tertian Plasmodium).—(1) Large size, after the development of pigment. (2) Number of *merozoites*, 12 to 24, arranged irregularly. (3) Presence of all stages in the peripheral blood. (4) Increased size of the infected erythrocyte. (5) Presence of Schüffner's "dots" (eosinophilic granules) in the infected erythrocytes.

Plasmodium malariæ.—(The Quartan Plasmodium).—(1) Medium size, after the development of pigment. (2) Number of *merozoites*, 6 to 12, and regular arrangement of the same. (3) Presence of all stages in the peripheral blood. (4) No enlargement of the infected erythrocyte. (5) Absence of Schüffner's "dots" in the infected erythrocyte.

Plasmodium falciparum.—(Tertian Estivo-autumnal Plasmodium).—(1) Small size, even when fully developed. (2) Number of *merozoites* 10 to 20, as a rule, small and arranged irregularly. (3) Only "ring forms" and young pigmented forms occur in the peripheral blood, as a rule, together with crescents (*gametes*) after the infection has persisted for several days. (4) Infected erythrocyte generally smaller than the normal erythrocytes. (5) Presence of Maurer's "dots" or basophilic granules. (6) Crescentic shape of the *gametes*.

Plasmodium falciparum quotidianum, the quotidian estivo-autumnal plasmodium, differs from *Plasmodium falciparum* in being much smaller at every stage in its development, while the *merozoites* vary in number from 6 to 18, the average being from 12 to 14. The "ring forms" are very minute, resembling in this respect the *piroplasma*.

Therapeutic Test.—As Osler well said, any fever which resists the action of quinine properly administered for more than four or five days is not malarial in character. This fact is used as a means of diagnosis when for any reason an examination of the blood is impossible, but quinine may reduce the temperature in diseases other than malaria. In some instances harm may be done, especially in typhoid fever, which often resembles the continued estivo-autumnal infections.

Differential Diagnosis of the Various Forms of Malarial Fever.—This is most quickly and scientifically made by an examination of the blood. In this way the entire life cycle of the tertian and quartan plasmodia may be studied, and the types of plasmodia easily differentiated. When an examination of the blood is impracticable, the clinical symptoms may be of service in distinguishing the various types; thus, a typical tertian or quartan infection is easily differentiated by the time of the occurrence of the paroxysm and the study of the temperature chart alone, but it is impossible to differentiate a double tertian infection from a quotidian estivo-autumnal infection in this way, and the mixed infections cannot be differentiated by the clinical symptoms only. The temperature chart in uncomplicated tertian estivo-autumnal fever is so characteristic that a differentiation of this form from other malaria infections can be easily made, but in all forms of malarial infection, the diagnosis should rest chiefly upon blood examinations. While it may not appear to be of great importance to be always able to differentiate the exact type of malarial infection present, it surely is so from a scientific standpoint, and is often so practically. Grave mistakes have been made in considering a severe estivo-autumnal infection as a mild tertian.

While in uncomplicated tertian and quartan malaria the examination of the blood may not be absolutely essential for diagnosis, in the estivo-autumnal infections, and especially in those presenting anomalous symptoms, such an examination is of the greatest service. In these cases the

presence in the blood of the small intracellular ring forms only, or of the crescents, demonstrates at once the nature of the infection.

The diagnosis of malarial fevers from other diseases which may closely resemble them is only possible, in many instances, by the use of the microscope. This is especially true of the estivo-autumnal infections which so often present anomalous symptoms that from a study of the clinical features alone a diagnosis cannot be made. There are a number of diseases with which malarial fevers may be confused.

Typhoid Fever.—Perhaps no other disease has been confused so often with malaria as has typhoid fever. Clinically, the confusion regarding these two diseases has much to excuse it. It is probable that a typical tertian or quartan infection is never suspected to be typhoid, or *vice versa*, but in the more irregular estivo-autumnal infections this mistake has often been made. In regions in which estivo-autumnal malaria is endemic or supposed to be, it is a common mistake to regard patients with typhoid fever as having this type of malaria. This is because many cases of estivo-autumnal infection present typhoid symptoms and a clinical differentiation is impossible. The mistake of considering a typhoid infection as malarial, after quinine has been administered for several days, is inexcusable, for there is no malarial fever which resists the action of quinine, when properly administered, for a period of six to eight days. If parasites are present in the blood, and the Widal test and blood cultures are negative, the diagnosis is established; cases of combined infection are rare. During the decline of the temperature in typhoid cases a marked intermittent temperature is common which resembles closely that of quotidian malarial infection. Chills may occur at this time and a diagnosis of malaria is made. Unless supported by the finding of malaria plasmodia in the blood, such a diagnosis is unjustifiable.

Yellow Fever. In regions in which yellow fever is endemic, the differentiation of malaria from this disease is often exceedingly difficult without a blood examination. The so-called "bilious remittent type" of estivo-autumnal malaria is especially apt to simulate yellow fever, there being a yellow tint of the skin, severe vomiting, sometimes of dark material resembling "black vomit," while albumin appears in the urine. A patient presenting such a clinical picture in a yellow fever region is almost always thought to have yellow fever, and in these cases an examination of the blood is of the greatest importance.

Tuberculosis.—In many cases the temperature chart of tuberculosis closely resembles that in quotidian malarial infections. There may be daily chills or chilly sensations, and the patient presents the facies so often observed in long-continued malarial infection. An examination of the sputum will generally result in finding tubercle bacilli, while physical examination shows pulmonary lesions. An examination of the blood is essential, as not infrequently patients with tuberculosis contract malaria.

Hepatic Abscess.—In regions where amœbic dysentery is endemic, patients with hepatic abscess may present symptoms which closely simulate those of malarial fever; there may be daily chills and a temperature curve which closely simulates that of some forms of estivo-autumnal

infection. The chief points in favor of hepatic abscess are enlargment of the liver and tenderness over the hepatic region, while the spleen is not enlarged. A history of dysentery can generally be obtained in cases of hepatic abscess. Examination of the blood will decide if malaria is present and a leukocytosis points to a hepatic abscess.

Ulcerative Endocarditis.—The temperature chart in ulcerative endocarditis often resembles that of quotidian malaria. Examination of the heart will generally suffice to determine the nature of such cases, and if not, an examination of the blood will decide the question.

Cerebral Apoplexy.—The differential diagnosis between the comatose pernicious form of malaria and cerebral apoplexy is often extremely difficult unless a blood examination be made. The main clinical points in arriving at a diagnosis of malaria are high fever, although this is not constant, the age of the patient, and the splenic enlargement. An examination of the blood should decide the question.

Sunstroke.—Especially in tropical or subtropical regions, certain forms of pernicious malaria very closely resemble sunstroke. In such regions the heat very often aggravates or brings on severe malarial paroxysms. It is therefore necessary to be sure in such cases whether or not malarial infection is present and a microscopic examination of the blood is often our only means of arriving at a diagnosis.

Dysentery.—Malaria may occur with dysentery, and as malarial infection can produce the symptoms of dysentery, it is important that a diagnosis be made in regions where dysentery is endemic. An examination of the blood is therefore essential in every case of dysentery occurring in such regions, as well as stool examinations.

Among other diseases which may be confused with malaria are septicemia, pyemia, diseases of the gall-bladder or ducts, acute suppurative processes in any of the viscera, pneumonia, and Weil's disease. In these a careful examination of the blood is essential in arriving at a diagnosis.

Prognosis.—While the prognosis in uncomplicated cases of tertian and quartan malaria is good, fatal cases of both these forms have occurred, especially the quartan variety. As regards the prognosis of the estivo-autumnal infections, certain factors such as locality, age, occupation, position in life, and physical condition must be considered.

In the tropics the prognosis in estivo-autumnal infections is much more grave than in temperate regions, and in certain local regions these fevers are much more fatal than in others. The prognosis is most grave at the extremes of life. It is more grave in the poor than in the well-to-do, in the case of individuals in ill health than in those who are well-nourished and healthy. Complications have much to do with the prognosis, among the most serious being the various forms of nephritis, tuberculosis, pneumonia, dysentery, and the infectious fevers. The prognosis in the pernicious varieties of estivo-autumnal infection should always be guarded, especially if the patient is seen after several severe paroxysms, although even then if treatment be vigorously instituted the patient may recover. However, the pernicious symptoms may last for several days, and despite all treatment, death ensue. The prognosis is very grave in

the cerebral forms, especially the comatose. In the algid form the prognosis is almost as grave as in the cerebral forms, and not a few die despite all treatment. The prognosis is very grave in the choleraic form and also the pneumonic. In the dysenteric form the prognosis is always grave, as the dysenteric symptoms have often masked those of malaria for a considerable time and treatment is not instituted until too late.

In *malarial cachexia* when a change of locality cannot be secured the prognosis is always grave, death resulting not so much from the malarial infection as from some complicating disease. While under proper treatment a great majority of cases of estivo-autumnal infection recover, unless quinine be administered for a long period, relapses invariably occur, and one of these may prove fatal. It may be stated as an axiom that the prognosis in tertian and quartan malaria is good, but in the estivo-autumnal infections it is always grave, as at any time during their course, pernicious symptoms may develop and prove fatal.

Prophylaxis.—We know the etiological factors and their method of transmission, and proper methods of prophylaxis have resulted in the disappearance of the infection from many localities. The discovery of the relation of the mosquito to the transmission of the malarial fevers placed their prophylaxis upon a scientific basis, and much has been accomplished by the destruction of these insects or by protecting man from their bites. If it were possible to destroy all malaria-carrying mosquitoes or kill all the plasmodia in the blood of infected individuals, we would prevent malarial infection in any locality. While either is theoretically possible, we know that in most instances it is practically impossible, and we are forced to combine methods looking both to the destruction of the plasmodia and the mosquitoes.

General Prophylaxis.—This may be considered under the following divisions: (1) Destruction of the mosquito; (2) isolation of the patient; (3) use of quinine; (4) proper treatment of initial infections and of carriers; (5) screening of houses; (6) education of the public.

1. *Destruction of the Mosquito.*—The mosquito is most easily destroyed during the larval stage. Sprinkling a thin layer of kerosene upon the surface of the water in which they breed is efficacious, not only killing the larvæ in the water, but the mosquitoes when in the act of depositing their eggs. The method is especially applicable to collections of water which cannot be drained and which are not very large. The quantity of kerosene used is approximately 1 ounce to 15 square feet of surface, and, as a rule, the application does not need to be renewed more than once a week. Collections of water thus treated should be frequently inspected, as the film of oil may be displaced by currents, winds, or by the movements of aquatic animals. This method should be depended upon only when it is impossible to drain or otherwise destroy the breeding places of mosquitoes. Light fuel oil is now generally used for this purpose instead of kerosene.

Other substances capable of killing the larvæ and which have sometimes been used in prophylaxis are sulphurous oxide, permanganate of potassium with hydrochloric acid, sulphate of iron or copper, corrosive sublimate, formalin, cresol, certain anilin dyes and coal tar. Most of these cannot

be used practically, the only ones really useful being kerosene or fuel oil. These cannot be employed in water used for drinking or culinary purposes, unless in large reservoirs where the water is drawn from the bottom.

The introduction of fish into reservoirs from which water is used for drinking purposes, and in which mosquitoes breed, has been tried with success. The fish principally used are carp and the common stickleback.

The most important of all methods of destroying the mosquito larvæ is by drainage of their breeding places, and this can be employed over large areas of country in which malaria is endemic. Experimentally it has proved to be of great service. In many regions in which the most virulent forms of malarial infection are endemic, drainage is feasible and can be carried out with but little trouble, although the expense is often a factor, and, as Celli says, "such methods for the destruction of the mosquitoes, while experimentally soluble, will only be practically so when economic interests desire it." Where drainage is impossible the breeding places of the mosquito may be filled in, and it is very important in malarious localities to fill up all depressions in the surface of the land that cannot be adequately drained. Swampy areas, if not too large, can be filled in, and one of the greatest sources of mosquitoes removed.

A valuable means in conjunction with draining and filling in, is the removal of shelter for the mosquitoes, such as in furnished by jungle, long grass, and vegetation within or along the banks of streams. The removal of the vines, which so often enclose the porches of houses in malarial localities, and ornamental shrubs will result in a great diminution in the number of mosquitoes.

The formation of mosquito brigades, suggested by Ross, is of great service. This consists in detailing a certain number of men to inspect the premises and destroy the larvæ in small breeding grounds which harbor the *Anophelina*, such as domestic water receptacles and tanks, the removal of small puddles in streets and yards, as well as empty tins, broken bottles, or anything in which water collects, and in which mosquitoes may breed. The region to be covered is divided into areas, each being under the supervision of men detailed for the purpose. Methods similar to this were pursued in Havana by Gorgas, resulting in the almost total disappearance of the yellow fever mosquito in that city. Garden wells, water barrels, and tanks should be covered, preferably with wire mosquito-netting, containing 18 meshes to the inch, thus preventing the laying of eggs and the development of the larvæ. If this is not possible, and the water is not used for drinking purposes, the surface should be sprinkled with oil.

In the adult stage the mosquito can be destroyed by various odors, fumes, or gases. Among the odors may be mentioned turpentine, menthol, and camphor. Among the fumes, tobacco, pyrethrum powder, and the fresh leaves of eucalyptus; while among the gases, sulphuric oxide is very efficacious. In using any of these agents the air of the room should be saturated, as otherwise the insect may be simply stunned, and revive when fresh air is admitted. The most useful of these agents is pyrethrum powder and sulphur which can be burned in rooms infected with mosquitoes. If sulphur is used the amount necessary may be ob-

tained by dividing the number of cubic feet in the room to be fumigated by 500, and reading the result in pounds. All metallic objects should be removed from the room as well as fine fabrics.

2. *Isolation of the Patient.*—If we place the infected individual where mosquitoes cannot obtain access to him the transmission of the infection is impossible. Theoretically, if every patient suffering from malaria could be screened from mosquitoes and properly treated, the disease would entirely disappear, but practically the disease is of such a character that even when no symptoms are present the parasites may be present in the blood and mosquitoes may become infected. In estivo-autumnal infections the crescentic form of the organism, which is intended to undergo its life cycle in the mosquito, is frequently present in the blood when there are no symptoms of malaria, so that it is obvious that we cannot in in this way entirely prevent malarial infection. Still the malarial fevers should be regarded as infectious and the patient should be isolated in a screened room. Not only is this of importance to others but also to the patient, for if he is not protected from mosquitoes he is in constant danger of reinfection. *Isolation* is of the greatest importance in the prophylaxis of malaria, and should be carried out, especially in regions where the more pernicious forms are endemic. Ross and Stephens also suggested as a method of prophylaxis the segregation of certain classes of the population. This applies especially to Europeans living in the tropics. They suggest that the European quarter should not be built in the midst of the native villages in malarious localities, but situated at some distance and surrounded by proper hygienic conditions, which it is often impossible to obtain among a native population.

3. *Use of Quinine.*—The use of quinine as a prophylactic measure is undoubtedly of service if the drug is properly administered. It acts by killing the plasmodia before the development of symptoms, by preventing the development of *gametes*, or preventing relapses. Quinine should be administered to all individuals harboring the malaria plasmodia and to all exposed to the bites of anopheline mosquitoes in localities where malaria is prevalent. The method of administration in prophylaxis differs with different observers. It should preferably be given in solution, in capsules or in freshly made tablets, and the dosage will vary with the class of individuals treated. It is now known that larger doses are required to prevent malarial infection than was formerly thought, and the writer believes that a daily dose of 1 gram (15 gr.) of quinine should be given, in two doses, one upon retiring and one in the morning. This dosage is recommended as a prophylactic in healthy individuals who have never suffered from malaria, but larger doses are necessary in individuals who are already infected, in order to prevent a relapse and the development of *gametes*, while "carriers" of malaria, *i. e.*, those having *gametes* in their blood, should be given 2 grams (30 gr.) of quinine daily until the *gametes* disappear.

The impression that quinine prophylaxis must extend throughout the year in malarial localities is erroneous, for in almost every locality these infections are more or less seasonal, and it is only in the malarial season that the use of quinine may be imperative. In temperate regions and

in the subtropics, for periods of from four to five months, the use of the drug as a prophylactic may be omitted with comparative safety.

Quinine prophylaxis is valuable in preventing malaria and the drug should be supplied by the State to those who are too poor to buy it, as is done in Italy and Greece. The results of quinine prophylaxis in Italy proved beyond question the value of this method, and Celli claims that the issue of quinine by Italy has saved no less than 7500 lives and that of 59,340 persons taking daily doses of quinine of 0.4 gm., only 5.8 per cent. developed malaria, including both initial infections and relapses.

4. *Treatment of Initial Infections and of "Carriers."*—A very large proportion of latent malarial infections are the result of improperly treated initial infections. While, in many instances, the plasmodia may be found in the blood for several days before the onset of the initial attack, most latent infections have been preceded by acute attacks of fever. The profession is largely to blame for these cases in civilized regions, for if the initial attack had been properly treated no plasmodia would have survived and the latent infections would have been prevented. The practice of regarding malarial infections as cured because symptoms have disappeared is a common and pernicious one, and is responsible for a large proportion of malarial disease. Nothing is more common than to see malarial patients walking about after only a few days of treatment, inquiry eliciting the fact that the physician has given no directions regarding the necessity of the continued use of quinine or directions for such use. All malarial infections are resistant to treatment; the mere disappearance of symptoms is no index of the entire destruction of the plasmodia present; and a continued course of quinine is necessary to rid the patient of even the mildest infection.

The proper treatment of these latent infections, or of malarial "carriers" as they may be called, is of the greatest prophylactic importance. In cases in which *gametes*, or the forms which undergo development in mosquitoes, have developed, treatment is much more difficult than when they are absent, as these forms are more resistant to quinine. The researches of Darling and of Thompson indicate that large doses of quinine administered daily will reduce the number of *gametes* to a non-infectious minimum, but it takes from 20 to 30 grains of quinine per day, for two, three, or four weeks, to do this, and thus, in many instances, treatment to be efficient is almost a cruelty to the patient. However, all latent malarial infections should be treated as acute infections, for these patients continually infect mosquitoes.

5. *Screening of Houses.*—The screening of habitations in regions in which malarial fevers are endemic is a most valuable measure, the objection to it being the expense involved, but the neglect of the measure is in the end more expensive. Copper wire should preferably be used in screening, or, if this cannot be obtained, ordinary iron wire screening covered with two coats of good paint to prevent rusting. The wire screening should contain 18 meshes to the inch.

6. *Education of the Public.*—All methods of prophylaxis depend for their success upon the support of the public, and it is the duty of the medical profession to offer every means available to the public for their

education in the prophylaxis of these fevers. Such educational measures should originate in the Boards of Health, and consist in addresses by qualified physicians; the issue of educational bulletins; the enlistment of the press, in the interests of publicity; and the notification of malaria to health authorities, in the same manner as any other infectious disease. Such notification would focus the attention of the public upon the immense harm done to a locality by the presence of malarial infection. The teaching of the essentials of prophylaxis in the public schools is a most important aid. The young are receptive and there is no better way of interesting the parents than by the instruction of the children.

Personal Prophylaxis.—By this we mean measures which the individual himself may take to prevent infection, or, in other words, to prevent being bitten by mosquitoes. If one is obliged to travel in malarial districts, the season of the year in which such fevers are less prevalent should be selected, if possible, and traveling should be done in the daytime. In selecting camp sites and sites for buildings, high, well-drained land should be chosen. If mosquitoes are numerous it is better to sleep above the ground floor. In tropical regions the use of punkas, or fans, as well as, where obtainable, electric fans, is serviceable in keeping away mosquitoes. For the protection of the hands and face odorous substances may be employed, these being smeared on the skin. Among the most useful are oil of citronella or pennyroyal, camphor, oil of eucalyptus, oil of anise, and kerosene. Pyrethrum powder should be burned before retiring, in rooms in which mosquitoes are present. Individuals in malarial localities should always sleep under a mosquito net.

One of the most important aids is the daily ingestion of 1 gram (15 gr.) of quinine. While this amount of the drug will not prevent malarial infection in some individuals it will, under ordinary circumstances, prevent infection in the vast majority if it is actually ingested. Most of the failures that have followed the use of the drug in this dosage are due to the fact that the drug was never ingested. One must see the drug actually swallowed before one can be sure that it is being taken and no statistics regarding the value of this method of prophylaxis are of any value unless the actual ingestion of the drug has been overseen by a responsible person.

Treatment.—This may be divided into hygienic and medicinal. While the medicinal is the most important, hygienic measures should always be combined. Fortunately, we have a specific which is generally successful, when properly administered, in curing the disease. There are rare instances in which it *seems* to be powerless to limit the course of malarial infection, but if it is administered in the proper manner it is efficient in these cases as in others. Certain individuals cannot absorb quinine through the stomach, but in such persons the hypodermic administration is effectual and thus it is that the successful treatment of malaria by quinine depends almost entirely upon the proper administration of the drug.

The mild malarial infections, as the tertian and quartan, tend toward spontaneous recovery so far as symptoms are concerned, but both of these types of malaria are more resistant to treatment, so far as actual cure is

concerned, than the estivo-autumnal infections, and this is especially true of infections with *Plasmodium vivax*. In many instances of infection by the tertian and quartan plasmodia, recovery may occur without medicinal measures, but these infections may become pernicious, and even if they do not, the occurrence of repeated paroxysms results in a diminution of the vitality of the patient, as evidenced by the anemia which invariably accompanies repeated attacks. Thus it is important that every malarial infection should be treated medicinally and not left for nature to cure.

Hygienic Treatment.—In all malarial infections, however mild, rest is most important, and the patient should be confined in bed until the active symptoms have disappeared. While this is not essential in some of the mildest tertian and quartan infections, it should always be followed in estivo-autumnal infection. Treatment by quinine is always much more effective when the patient is confined to bed, recovery is always more rapid and permanent, and the danger of pernicious symptoms is much lessened. In all cases of malarial infection the sick-room should be, if possible, in an upper story, well ventilated and thoroughly screened, thus limiting the chances of infection to others.

The *diet* should be light while active symptoms are present, consisting of milk, soups, custards, soft-boiled eggs, etc. A light diet should be given until the temperature has been normal for at least a day, and then a more liberal diet is indicated. The more nutritious the diet is the better, as in many cases the debility and anemia are marked.

It is well to secure a complete evacuation of the bowels with or before the administration of quinine. The administration of calomel until the bowels move freely renders the action of quinine much more efficient. It hastens and favors the absorption of the drug.

Medicinal Treatment.—In the vast majority of malarial infections but one drug need be considered, that is *quinine*, and by quinine any derivative of cinchona bark is meant. In considering its uses the following points are discussed: (1) Its action upon the plasmodia; (2) the choice of preparation; (3) the time of administration; (4) the methods of administration; (5) the dosage; and (6) contraindications.

1. *The Action of Quinine upon the Malaria Plasmodia.*—Quinine acts upon malarial infections by directly destroying the plasmodia.

Plasmodium vivax.—(Tertian Plasmodium).—In the living specimen the administration of quinine in therapeutic doses causes an initial stimulation of amœboid movement in the parasite, followed by a decrease in activity, and finally cessation of motion; granular degeneration of the cytoplasm follows, and eventually the parasite undergoes fragmentation; extrusion of these fragments from the infected erythrocyte follows. In organisms not destroyed, there is less pigment developed and sporulation is atypical, in that a smaller number of *merozoites* are produced. The *gametes* present no changes in morphology after the administration of quinine, but none develop if sufficient of the drug be administered at the beginning of the infection.

In stained specimens the following changes may be noted after the administration of quinine: The cytoplasm stains a more intense blue,

the chromatin of the nucleus stains an almost black color, and fragmentation of the parasite is clearly demonstrated. Atypical sporulation, as evidenced by a smaller number of *merozoites* and the absence of chromatin from many of the *merozoites*, is frequently observed. Similar changes are observed in stained specimens of young *gametes*, but the fully developed *gametes* present no morphological changes.

Plasmodium malariæ.—(Quartan Parasite).—The action of quinine is identical with that observed in the tertian plasmodium and the writer has not observed any morphological evidence that this species is more resistant to quinine than the tertian parasite.

Plasmodium falciparum and Plasmodium falciparum quotidianum. (Tertian and Quotidian Estivo-autumnal Parasites.)—In the fresh blood the organisms appear more refractive after quinine has been administered, and at first amœboid activity is greatly stimulated, but later is entirely lost. The cytoplasm appears more granular than normal, and in the pigmented parasites marked evidences of degeneration are observed. In stained specimens the cytoplasm stains intensely blue; while the chromatin stains dark violet instead of the usual ruby-red color. Extrusion of the chromatin is sometimes observed, while the vesicular portion of the nucleus is absent. In the pigmented and sporulating parasites the changes are similar to those in the tertian and quartan parasites, consisting of a granular degeneration of the cytoplasm which stains an intense blue; decrease in the amount and atypical staining of the nuclear chromatin; fragmentation of the plasmodia and decrease in the number of *merozoites* produced in the parasites not killed by the drug. The writer has never observed any morphological changes in the crescents or *gametes* when fully developed, but in the intracellular early stage quinine is capable of killing them. Intracorpuscular conjugation appears to be prevented by quinine early in an infection.

In summary, quinine affects the malaria plasmodia at every stage in their development up to the presporulating stage and the fully developed *gamete*. If the drug acts directly upon the *merozoites* the vast majority are destroyed, and those that escape are apt to be badly crippled, as shown by atypical development and the decrease in the number of spores. The idea that quinine cannot act upon the plasmodia after they have invaded the erythrocytes is erroneous, and it is my opinion that the drug greatly hinders the development of the parasites while they are intracellular and thus produces the many atypical sporulating forms observed after its administration. It has not been proved, and there is little ground for believing, that the exhibition, for a long period, of doses of quinine insufficient to kill the plasmodia may result in the development of quinine-fast strains and that these strains furnish the explanation for the cases of malaria that are very resistant to the drug and relapse frequently despite all treatment.

2. *Choice of Preparation.*—Of the many salts of quinine, but three are really deserving of attention, in that they are generally available and of practical use. These are the sulphate, the dihydrochloride, and the tannate. For general use the sulphate is usually preferred, as it is cheap and reliable, but it has the disadvantage of being very insoluble and irri-

tating to the stomach. The dihydrochloride is very soluble (1 part to 0.96 parts of water) and should always be used when the drug is to be administered hypodermically. The tannate is excellent for administration to children, put up with chocolate in the form of troches or a confection. Nardelli claims that this salt is the best for use as a prophylactic as it is absorbed more slowly and is more completely oxidized than any other salt of quinine; this opinion is concurred in by Celli, who states that it is the ideal salt for prophylactic purposes. Fletcher obtained very poor results with this salt of quinine in the treatment of malaria in natives of the Federated Malay States.

3. *Time of Administration.*—The drug acts upon practically every stage of development of the parasites, being most effective upon the *merozoites* and the young intracellular forms. It follows that the best results will be obtained if the drug is present in the blood continually, and this is best secured by the administration of quinine at regular intervals throughout the twenty-four hours. While good results are secured in uncomplicated tertian and quartan infections by one large dose just before the expected time of sporulation, they cannot be compared to the results obtained by the interrupted administration of the drug, and in estivo-autumnal infections the interrupted method is the only one that should ever be adopted. The discomfort to the patient is much less when the drug is given at regular intervals and the remedial results are much more lasting. To secure the best results quinine should be administered in *acute* attacks every three or four hours, in the proper dosage, until the symptoms have disappeared, when it should be administered morning and evening for some days and then as recommended in discussing the dosage of the drug.

4. *Methods of Administration.*—This may be by the mouth, by the rectum, subcutaneously, intramuscularly, and intravenously.

By the Mouth.—This is the usual method and, with the exception of pernicious cases, there are very few instances in which the drug cannot be administered in this way with good results. By the mouth, quinine may be administered in solution, capsules, wafers, pills, troches, and a confection. Pills should never be administered, as they are often insoluble. The same criticism applies to tablets and troches, unless one is sure that they are freshly made. It is best to give the drug in solution, if possible, the sulphate being used and dissolved by adding a drop of dilute hydrochloric acid to each 0.065 gm. (gr. j) of the drug. If, for any reason, the solution cannot be employed, capsules or wafers are satisfactory, the chief objection being that the drug is liberated *en masse* in the stomach and may prove irritating. However, this may be disregarded from a practical standpoint. In patients who cannot take the sulphate, and in children, the use of troches of the tannate of quinine is indicated.

Rectal Administration.—This method is only mentioned to be condemned, as it is practically useless and very painful.

Subcutaneously.—This method should be abandoned. It has been repeatedly shown that when the drug is introduced in the usual dose in the subcutaneous tissue or intramuscularly, a coagulum results, the greater part of the dose becoming useless, while there is always danger of abscess

formation, and permanent indurations are sometimes produced. Absorption and oxidation of the drug are less when thus introduced than when taken by the mouth, so there is no good reason for this method save in those very rare instances in which the drug cannot be taken by the mouth, and then in my opinion the intravenous method is preferable. If, however, this is the only way in which quinine can be administered, it is much better to give it intramuscularly than subcutaneously.

Intramuscularly.—The salt to be used in any hypodermic method of administration should be easily soluble and for this the dihydrochloride is the best. The following solution should be used for injection:

℞—Quinine dihydrochloride . . . . . 5 gm. (gr. lxxv)
Normal salt solution . . . . . 10 gm. (℥iiss)

In this solution 1 cc. (♏xv) contains 0.5 gm. (gr. viiss) of the drug. The required amount is diluted three or four times with normal saline solution, sterilized, and injected deep into the muscle, the glutei being generally selected.

In giving quinine intramuscularly or intravenously, the utmost care should be taken to secure strict asepsis. The syringe should be a glass one, properly graduated, and sterilized just before use. The salt solution should be made from freshly distilled water and also sterilized. The skin over the region to be injected should be washed with hot water and painted with tincture of iodine. The quinine should be dissolved in a small amount of absolute alcohol which practically sterilizes it, and should then be placed in the requisite amount of salt solution and sterilized. The fluid should be injected slowly, and after the needle is withdrawn the site should be touched with tincture of iodine.

The intramuscular injection of quinine was quite popular with army surgeons serving in malarial regions during the World War but many bad results followed its use, as abscess formation and infection of the injected area, and Fletcher[1] has shown that the drug is not absorbed as quickly when administered in this manner as by the mouth, and that the results are no better, if as good; the idea that quinine thus injected forms a reservoir which feeds the drug to the peripheral blood he has shown to be false. He recommends, and the writer agrees with him, that the intramuscular injection of quinine be reserved for patients dangerously ill with malaria, for those who are comatose, and for those who cannot retain the drug when taken by the mouth. Personally, I prefer the intravenous administration of the drug in individuals who are comatose or in whom the symptoms are of pernicious character.

Intravenous Injection.—This was introduced by Baccelli, and it is the one which has proved most useful whenever it is desired to secure the most prompt effects of the drug, as in pernicious infections. This method should be reserved for pernicious infections or for patients who cannot take quinine by the mouth, but further research may prove that it is possible to kill all the plasmodia by one or two intravenous injections of some preparation of the drug, or, perhaps, by some new derivative of

[1] *Notes on the Treatment of Malaria with the Alkaloids of Cinchona*, London, 1923.

quinine, or other drug, and if so the intravenous administration will undoubtedly replace the other methods.

The solution usually recommended is that of Baccelli, containing 1 gm. of dihydrochloride of quinine and 10 cc. of normal salt solution, the entire amount being injected into a vein. While thousands of cases of malaria have been thus treated with good results, some deaths have occurred, and it has been generally accepted that these deaths were due to the great concentration of the drug. Accordingly it is advised that Baccelli's solution be diluted at least in the proportion of 1 part of quinine to 250 parts of normal salt solution as follows:

℞—Quinine dihydrochloride . . . . . 1 gm. (gr. xv)
Normal saline solution . . . . . 250 gm. (℥xvi)

The salt solution must be made of freshly distilled water, the mixture sterilized before use, and injected while lukewarm.

The most careful precautions should be taken to maintain asepsis. The solution should be placed in a glass vessel of suitable capacity, open at the top, connected with a rubber tube in which is a glass window, and to which is attached a stop-cock and a suitable needle. The whole should have been sterilized before the solution is put into the vessel, a small piece of absorbent cotton being placed at the bottom of the container over the entrance of the rubber tubing. The skin over a large vein of the forearm is washed with hot water and painted with tincture of iodine. The vessel containing the quinine solution is elevated and a little of the solution allowed to flow through the tube, thus filling the needle, which is now introduced through the skin over the vein and then passed directly into the vein, being careful to keep the needle as nearly parallel with the forearm as possible. The solution is now allowed to flow into the vein slowly, governing the flow with the pressure of the finger on the tube or by the stop-cock. The entire amount of quinine solution should be injected with the exception of a few cubic centimeters left in the irrigator. The needle is then withdrawn, the site of the puncture painted with tincture of iodine, and a collodion dressing applied. The quinine is best dissolved in a small amount of absolute alcohol before it is added to the salt solution. This method appears to be devoid of danger. As quinine is a heart depressant, it is well to give strychnine hypodermically just before the injection.

5. *The Dosage of Quinine.*—It is probably true that there is no other drug which has been more abused as regards dosage than quinine. Almost invariably the chief fault has consisted in giving too much of it, doses of from 5 to 6 gm. (gr. 75 to 90) not infrequently being given during twenty-four hours. The use of such large amounts is never required and instead of doing good they greatly increase the discomfort of the patient. The writer has never observed a case of malarial fever in which it was necessary to give over 2.5 gm. (gr. xl) of quinine in twenty-four hours, and 2 gm. (gr. xxx) of the drug, properly administered during the twenty-four hours, and continued for three or four days, is sufficient for any ordinary case of estivo-autumnal malaria, while 1.3 gm. (gr. xx), given just before the paroxysm, and continued

in divided doses through the twenty-four hours for the next few days, will be sufficient for most cases of tertian and quartan infection, so far as the symptoms are concerned.

General Scheme of Treatment.—The malarial infections vary so much in their severity and resistance to treatment, that it is not wise to prescribe a routine treatment in all cases but, in the vast majority, the following rules will be found useful and the results, in the writer's experience, have been most excellent.

In *tertian* and *quartan* infections, during the acute attack, quinine should be administered in 0.32 gm. (gr. v) doses every three hours, until from 1.3 gm. (gr. xx) to 2 gms. (gr. xxx) have been given and this daily dose continued until symptoms have disappeared. After the disappearance of symptoms at least 0.65 gm. (gr. x) should be taken daily in equal divided doses morning and evening, for at least three months. This dosage seems large but these infections are very resistant and usually relapse unless treatment is continued for the period mentioned.

In *estivo-autumnal* infections, in which the symptoms are not pernicious in character, quinine should be administered by mouth in solution or soluble tablets, and 2 gm. (gr. xxx) should be given, in divided doses, at intervals of three or four hours, every day until symptoms have disappeared. After this the drug should be continued for at least two weeks in doses of 1 gm. (gr. xv), in two equal doses morning and evening, and for the succeeding two months the drug should be given daily in 0.65 gm. (gr. x) doses, 0.325 gm. (gr. v) morning and evening, or, if preferred, in a single dose of 0.65 gm. (gr. x) upon retiring each night.

If quinine is given in the manner described we may expect a cure in most cases of uncomplicated malaria, but unless a rigorous method of keeping up treatment is adopted, relapses almost invariably occur and eventually the patient will become a *gamete* carrier.

The treatment of *latent* and *recurrent* cases is exactly that of acute cases so long as plasmodia are in the blood, and then a course of quinine should be given for two or three months, as already described.

The treatment of "*gamete carriers*" is an open question. Darling and Thompson agree in stating that large doses of quinine will reduce the *gametes* in the peripheral blood to a non-infectious minimum, and eventually cause their disappearance. The amount of quinine required to accomplish this is large, 2 gm. (gr. xxx) every day for three or four weeks being recommended by Thompson. All *gamete* carriers should be thus treated, if it be possible.

When intravenous treatment is used the dose should be from 0.5 to 1 gm. (gr. viiss to xv), and if no improvement occurs in five or six hours, the dose should be repeated. As a rule, if the drug is going to prove effective a marked improvement is noted within that time.

In children the dose should be proportioned to age. Under one year of age the usual dose is 0.032 gm. to 0.065 gm. (gr. ss to j), repeated as in an adult. In older children the drug is well borne, and in pernicious infections proportionately larger doses may be given.

Contraindications to Quinine.—In rare instances the use of quinine is contraindicated because of some idiosyncrasy to the drug. In some

people this drug acts as a violent poison and some substitute must be employed. If the use of quinine is followed by amaurosis, deafness, dyspnœa, syncope, hematuria, or hemoglobinuria, it should be discontinued, or if there is a clear history of such complications it should not be given. Pregnancy is not a contraindication to the use of quinine, although often stated to be so. The fear that the drug will cause abortion is not well-founded, for if carefully given the risk is not as great as if the malarial infection is allowed to continue. In malaria presenting pernic ous symptoms in pregnant women, quinine should be given intravenously, for the mother's life is endangered and it is justifiable to disregard that of the child.

Substitutes for Quinine.—Although numerous substitutes for quinine have been announced, not one of them is as efficient as the drug itself. *Phenocoll* is sometimes useful in tertian and quartan infections, but should not be used in estivo-autumnal malaria. The dose is from 1 to 3 gm. (gr. xv to xlv), distributed over the twenty-four hours. It is a heart depressant, and for this reason its administration should be carefully watched. *Methylene blue (medicinal)* is a useful drug in milder infections, but in severe estivo-autumnal malaria is of little value. Its use is not without danger, as in improper dosage it may produce strangury, albuminuria, and severe diarrhœa. The dose, in capsule with a little powdered nutmeg, varies from 0.15 to 0.2 gm. (gr. iiss to iij), every four hours. The patient should be warned that the urine will be colored blue. Some proprietary salts of quinine, as *euchinin*, *salochinin*, and *aristochin*, are useful substitutes, but are not as efficient, and are expensive. Their use is not without danger, and symptoms are produced much like those from quinine.

Arsphenamine and *neoarsphenamine* have been urged as specifics for malaria. The most reliable investigations appear to prove that in tertian malaria they are efficient, but useless in quartan and estivo-autumnal infections. *Atoxyl* has been experimented with in malaria, and found not only useless but dangerous.

Treatment of Special Symptoms.—During the *cold* stage of the attack, the external application of heat in some form is grateful, while in the *warm* stage great relief is afforded by sponging with tepid or cold water. High temperature should always be controlled by a bath, and the physician who uses antipyretics for this purpose submits his patient to an unnecessary danger. If nervousness is marked or the headache is very severe a hypodermic dose of morphia may be given. Symptoms of collapse, which usually appear during the decline in the fever, should be combated by the external application of heat, strong coffee and the subcutaneous use of normal salt solution. Atropine is useful in these cases. In pernicious infections, after quinine has been administered intravenously, the patient should be treated symptomatically. Collapse should be treated as indicated; in the *choleraic* form, opium should be administered to check the diarrhœa, and normal salt solution injected intravenously or subcutaneously, in addition to the ordinary use of stimulants. Severe vomiting may be treated by mustard plasters over the epigastrium,

the sucking of cracked ice, and the hypodermic injection of small doses of morphine.

Treatment of Malarial Cachexia.—The occurrence of malarial cachexia in a person who has been treated for the acute attacks of malaria preceding the cachexia is a reproach to the physician, for had proper treatment been given the conditions following numerous relapses could not have occurred. The best treatment of malarial cachexia is removal to a non-malarial locality, preferably to a high, dry region, with a bracing climate. The administration of tonics and proper hygiene regarding clothing, exercise, and food are of great importance. Quinine should be administered as long as the patient is exposed to reinfection or plasmodia can be demonstrated in the blood. The food should be nutritious and the patient urged to eat if the appetite is poor. The administration of Warburg's tincture is often of service, not so much because of the small amount of quinine it contains but for its tonic properties.

In conclusion, no substitute for quinine can equal it in the treatment of malaria, and in the worst cases the proper administration of this drug will result in prompt recovery, provided the patient be seen in time. There are one or two substitutes which may be used in very rare instances in which quinine is contraindicated, but the writer believes with Osler, that, "the physician who at this day cannot treat malarial fever successfully with quinine, should abandon the practice of medicine."

CHAPTER XII

BLACKWATER FEVER*

By J. W. W. STEPHENS, M.D. (Cantab.), F. R. S.

Introduction.—In my opinion, blackwater fever, wherever seen, is one and the same condition, and the symptoms vary in one and the same district from insignificant to most grave and fatal. I do not believe that mild cases are due to one cause (quinine hemoglobinuria in malarials) and severe cases to some other cause or causes. The main symptoms are: (1) hemoglobinuria, (2) bilious vomiting, (3) jaundice, and (4) fever.

Geographical Distribution.—In general terms its occurrence coincides with that of intense malarial infection.

Etiology.—Malaria Factor.—1. The distribution of this disease and of intense malaria is identical, and this becomes more and more clear as our knowledge of the distribution of the disease becomes more extensive. One of the best tests of the existence of severe malaria in a country is the endemic index (parasite rate) of native children, as used originally by Stephens and Christophers. One example must suffice; the endemic index on many tea gardens in the Duars, Bengal, approaches 100 per cent., and the conditions of life are such that *continuous* infection of Europeans with malaria is the normal state of things. Blackwater fever is there a common disease. The endemic index of the Tonkin Delta Provinces as a whole is 3.17 per cent. (in certain regions rising to 19 per cent.), and blackwater fever is exceptional there, but in the Upper Tonkin provinces as a whole the endemic index is 31.86 per cent., in some districts rising to 43 per cent., and there blackwater fever is frequent.

2. Blackwater fever is usually but perhaps not always associated with a high rate of prevalence of the malignant tertian parasite. In Upper Tonkin (Sonta province) the malignant tertian rate is 71 per cent., while in the Tonkin Delta the malignant tertian rate is 10 per cent.

3. The association of malaria and blackwater fever was shown by their frequency in Americans and Europeans respectively in the Panama Canal Zone during the construction of the Canal. Charts published by me in 1913 showed that the unprotected Europeans suffered far more from malaria than the protected Americans. As regards blackwater fever the average rate was four times as great in Europeans as in Americans from 1905 to 1909, in 1909 more than twenty times as great, and from 1910 to 1913 thirteen times as great.

4. The actual findings in regard to parasites as deduced by me from nearly 200 cases in which definite statements are made are the following:

Day before hemoglobinuria.		Day of hemoglobinuria.		Day after hemoglobinuria.	
Cases.	Positive.	Cases.	Positive.	Cases.	Positive.
116	88	100	50	76	13
78 per cent.		50 per cent.		17 per cent.	

* Bibliographies are given in C. Mense (Handbuch der Tropenkrankheiten, 3d edition, Leipzig, 1924, vol. 3) and J. G. Thomson (Researches on Blackwater Fever in Southern Rhodesia, London School of Tropical Medicine, Research Memoir Series, 1924, vol. 6).

The following data of Deeks and James (1911) in regard to malaria parasites are also instructive:

	Cases.	Positive.	Percentage.
Amœbic dysentery	260	48	18.4
Liver abscess	70	7	10.0
Typhoid fever	33	4	12.0
Blackwater present on admission	113	27	23.8
Blackwater onset after admission	102	60	59.8
Malaria	40,928	23,410	58.0

5. Seeing that parasites rapidly disappear in blackwater fever evidence of malaria infection may still be got from the pigmented leukocytes. Christophers and Bentley (1908) give the following example:

	First day.		Second Day.		Fourth to sixth day.	
	Cases.	Positive.	Cases.	Positive.	Cases.	Positive.
Parasites	10	6	7	0	10	1
Pigment	10	8	7	6	10	4

6. *Splenic Puncture.*—Barrat and Yorke (1909) found no parasites or pigment in 6 cases, whereas Christophers and Bentley (1908) found pigment or parasites in 4 of 5 cases. Barrat and Yorke in 2 cases of "malaria" found neither parasites nor pigment by spleen puncture.

7. *Postmortem Evidence.*—From an analysis of 39 cases in which definite statements were made as to the presence or absence of malaria pigment it appears that pigment was found in 32, *i. e.*, in 82 per cent.

8. Three instances have been given by authors as examples of countries where malaria exists, but no blackwater fever, viz., Egypt, Ceylon, and the Philippines. It is true that there is no blackwater fever in Egypt, but neither does malaria occur there, or, at any rate, to any appreciable extent, *e. g.*, during three months' work at the large Kasr-el-Ainy Hospital in Cairo, I saw only 2 cases of malaria, and both these had come from the Sudan. In regard to Ceylon and the Philippines, blackwater fever *does* exist in both these countries; but as to the frequency thereof we require further information. Finally, it is quite possible that the endemic index of a country might be very high and yet the mode of living of susceptible Europeans such that they would not contract malaria or contract it repeatedly.

Spirochetes have been recorded in cases of blackwater fever from the Philippines (blood of an East Indian), from Sumatra (with simple tertian parasites) and in a few cases from the Congo. In the two latter localities epidemic jaundice also prevailed. Others have searched in vain for spirochetes in blackwater cases.

The Quinine Factor.—It is now, generally admitted that quinine *can* produce hemoglobinuria. As to its mode of action Barrat and Yorke (1909) calculate that it does not act directly, as to produce appreciable hemolysis of oxalated red cells in vitro a 0.5 per cent. solution of bihydrochloride is required, implying in the body, with a blood volume of 5000 cc., a dose of 25 grams. The maximum concentration of quinine in the blood *immediately* after an *intravenous* injection is 1 in 20,000. The attack appears to ensue about three hours after taking a dose, it may be of only a fraction of a grain. In other cases quinine at least as an immediate

cause can be excluded. We might hazard the surmise that the prevalence of blackwater fever in a white malaria-infected community is proportionate to the amount of quinine consumed. According to Plehn (1918) quinine excretion by the kidneys is much higher in non-quinine than in habitual quinine takers.

Frequently there is a history of exposure to the sun, unwonted exercise, fatigue, chill, alcoholism, change of locality, etc.

Pathology.—The *spleen* is enlarged, with an average weight of 400 gm., which may exceed 1000 gm. Perisplenitis is constant. The Malpighian bodies are prominent and white (sago-grains) due to endothelial proliferation, but in parts they may be necrosed. Necrosis of the pulp may also occur. Immense phagocytes crowded with nuclear remains, cell débris, red cells and leukocytes occur in the necrosed areas. Auto-agglutination, hemolysis and phagocytosis of red cells may be seen in the dilated sinuses. An iron-free pigment and the "free" iron golden-yellow pigment hemosiderin also occur. The Prussian blue reaction for the latter shows granules in the cells or a diffuse color only is given. Pigmented leukocytes and parasites may be found postmortem when absent from the blood during life. Melanin is usually abundant, but in some cases it can only be found after long search, if at all, although parasites may have been found during life.

The *kidneys* are usually a little enlarged and on section the medulla may show distinct brownish radiating lines, due to deposits in the tubuli recti, and the cortex brown dots. The microscopic changes are not constant but the following may be seen: The *glomeruli* show (*a*) distention, and (*b*) varying amounts of albuminous exudates, granules, or "altered hemoglobin" globules between the tuft and the capsule. The *tubuli contorti* show (*a*) dilatation and flattening of the epithelium, (*b*) the epithelium granular and slightly swollen, or (*c*) distinctly necrotic, the nuclei of the regenerating epithelium showing mitotic figures; (*d*) œdema of the connective tissue and invasion of migratory cells (nephritis), (*e*) the *lumen* of the tubules practically always contains a finely granular coagulum of albuminous material or brownish globules of "altered hemoglobin" up to 5 μ in diameter, with desquamated cells scanty or numerous. This granular material is probably secreted by the epithelium of the tubules. By some authors these granules have been found to give the iron reaction, by others not, the difference possibly depending upon the length of time that has elapsed since their formation; Stieda records granules giving a free iron reaction in the epithelium itself.

The *tubuli recti* show (*a*) plugs or casts of dark reddish-brown, granular material (altered hemoglobin) 40 to 80 μ in diameter; sometimes these plugs appear to be hollow. The granules of which they consist are not larger than those in the convoluted tubes. (*b*) The epithelium is generally unaltered, but there may be a variable amount of desquamated cells in the lumen and separation of epithelium from the basement membrane.

The *liver* is usually somewhat enlarged, and averages 2000 gm. in weight. Necrosis central, focal or widespread, accompanied by fatty degeneration is commonly present. The liver cells contain more or

less golden-yellow pigment (hemosiderin), biliverdin and a yellow iron-free pigment. The capillaries are often dilated with blood, and may contain agglutinated red cells and masses of mononuclear leukocytes. Thrombosis of the sublobular veins occurs. Melanin, red cells and cellular débris occur in free phagocytes and in Kupffer's stellate cells. The bile capillaries are generally distended with plugs of yellowish or greenish material. The gall-bladder contains thick tarry bile.

The *bone-marrow* has a color uniformly red or purplish or mottled when the fat cells have not been entirely replaced by the marrow cells. It is nearly always hyperplastic (mainly, however, erythroblastic). Large phagocytes containing melanin, nuclear fragments, and red blood cells are found. A practically constant and striking change is the great relative increase in eosinophile cells (mononuclear and polynuclear, and the abundance of normoblasts and megaloblasts— Whipple). Melanin is always (?) found, though careful search may be necessary.

The *brain* is usually pale, but shows no parasites or pigment unless the blackwater fever has been immediately preceded by acute malaria with parasites in the blood, when much pigment and many parasites are found in the capillaries.

Symptoms.—Prodromal Illness.—This is nearly always present and cannot be distinguished from an ordinary attack of malarial fever. It usually lasts some days, and the patient has nearly always already treated himself with much quinine before being seen. Over 80 per cent. of Deek's and James' cases had previous admissions for fever (malaria).

Fever.—The attack begins with a rigor in about half the cases, the temperature rising rapidly to about 103° to 105° F., or even higher. In some cases the rise is not above 100° F. and in other cases the course is found to be afebrile. The temperature curve is usually an atypical, irregular one, intermittent or remittent, but in other cases the curve is distinctly quotidian or tertian. In a day or so, or even in a few hours, as the urine clears the temperature falls, and there is more or less profuse sweating and intense weakness. The attack is usually accompanied by great restlessness, mental anxiety, shortness of breath, and pains in various regions, *e. g.*, the loins and epigastrium. Rigors may occur repeatedly during the course of the fever and hyperpyrexia may ensue with fatal results.

Posthemoglobinuric Fever.—Occasionally after cessation of all the usual symptoms, *e. g.* hemoglobinuria, fever with evening rises of 101° to 102° F. or more may ensue and last for some weeks, even ending in hyperpyrexia. What this fever is due to is unknown, possibly in some cases to a secondary infection.

Hemoglobinuria.—Occasionally this is the first indication the patient has that he is really unwell. There may be practically no other sign. These apparently apyretic cases, "quinine hemoglobinuria," are considered by some as distinct from blackwater fever proper, but in our opinion no line can be drawn between these cases and the severe ones with intense initial rigor and subsequent grave symptoms. Usually after a shivering fit there is an urgent desire to pass water, and the patient then becomes aware that his urine is "red." The hemoglobinuria may be confined

solely to the first urine passed; usually it lasts one or more days but exceptionally for over a week. The hemoglobin may either gradually disappear, or when decreasing may increase again or after clearing may return with a fresh access of fever following a dose of quinine or from unknown causes. As many as eleven recurrences may follow, and in certain cases they can be produced at will by quinine. They may occur twelve days after cessation of the original hemoglobinuria. In grave cases oliguria develops, gradually passing into anuria or the condition may supervene suddenly. Suppression may ensue even if the urine passed is normal.

Vomiting.—Frequent retching, attended in nearly all severe cases by bilious vomiting, is a distressing symptom, the vomitus consisting of dark green bile. It is accompanied by pain in the epigastrium, and if prolonged produces great exhaustion, and if persistent hiccough occurs the prognosis is bad. Thirst and restlessness are often pronounced and tympanites is common and distressing.

Icterus.—This occurs in the great majority of cases. It sets in within twenty-four hours after the attack, and is more or less intense, the conjunctivæ and the skin over the whole body becoming a lemon yellow color. In grave cases it is persistent, in slight cases but transient.

Constipation is usually present. The spleen and liver are enlarged and the enlargement of the former appears to run parallel with the severity of the attack. In mild cases the fever, headache, vomiting, and other symptoms gradually subside as the urine clears. In grave cases the fever recurs or persists, the jaundice deepens, thirst is intolerable, and the vomiting is incessant. Hiccough, oliguria leading to anuria, attacks of profuse diarrhœa (reddish), dyspnœa, great restlessness, delirium or convulsions, somnolence, and prostration, are conditions which may dominate the scene in particular cases. Death may result from (1) anuria, (2) heart failure, or (3) hyperpyrexia. The mortality can be estimated roughly as about 20 per cent.

Second attacks occur in about 10 to 20 per cent. of cases. About 60 per cent. occur within the year and 30 per cent within six months. Ten or more attacks may occur.

Urine.—The reaction may be neutral, acid, or alkaline; the specific gravity varies between 1.002 and 1.025. In color it may vary from a very dark red-brown or almost black porter-color to a brownish-yellow. Characteristic is the suspended matter which it contains. The quantity varies from $\frac{1}{60}$ to $\frac{1}{6}$ of a column. This suspended matter (altered hemoglobin) consists of a granular matter of variable color, chocolate, brownish-black, light yellow, whitish, and of variable amount. Besides the granular matter, granular casts, 15 to 200μ long, 3 to 25μ broad (of the same material), embedded in a hyaline matrix, epithelial casts and masses, and free epithelial cells occur in varying amounts and not uncommonly a few red blood cells and rarely pus cells and bacilli. The size of the granules varies from 0.5 to 5μ in diameter and they are brownish in color. In cases of suppression the granular casts are larger, 100 to 150μ by 40 to 60μ, and the granules are coarser and of a dark, reddish-brown color. The urine usually gives the bands of oxyhemoglobin and sometimes

of methemoglobin also, the latter it is said only on standing (? acid hematin). Occasionally a brownish-yellow pigment convertible to hemochromogen on boiling with alkali replaces the oxyhemoglobin. Urobilin is commonly present. Sorensen (1914) considers that a urobilin reaction, in a dilution of 1 to 25 or more in tubes of 9.5 mm. thick in the urine of malaria cases is prognostic of a blackwater attack. Albuminuria may precede the hemoglobinuria and follow it for a day or much longer. A peculiarity of the urine is the length of time it resists putrefactive changes. The percentage of hemoglobin in the urine expressed in terms of red cells dissolved in water may reach a value of 5 per cent. The total hemoglobin passed in terms of red cells may reach a value of about 5 ounces. From the red cell count (and the total blood volume, assuming this to remain constant), it can be calculated that about ten times this amount of red cells is destroyed in the body (liver, spleen, etc.).

Bile pigment is usually not detected. In rare cases it may replace hemoglobin. Bile salts are said to be absent. Acetone and diacetic acid may be present. The chlorides may fall to a tenth of normal. The urea, during an oliguria of 30 cc., gave a value of 490 mgms. per 100 cc. (the blood urea at the same time being 480).

Feces.—Red or black tarry stools may occur. Urobilin is greatly increased; bile salts and pigment may be present.

Blood.—The red cells may fall below 1,000,000 and the hemoglobin to about 20 per cent. The blood has lost its viscosity so that a good film is often difficult to make. Hemoglobinemia precedes the hemoglobinuria but it rapidly disappears. The values in terms of red cells dissolved in water may be for health 0.25, for malaria 0.31 and for blackwater 0.95. Methemoglobinemia may occur and bilirubinemia is not uncommon. Data as to urobilinogen are lacking through urobilinemia is on record.

Morphology.—Some hours or days after the onset there occur: (1) Schistocytes, (2) poikilocytes (1 per cent.), (3) shadow cells, large or small, staining at the periphery only (1 per cent), (4) anemic cells, normal or pear-shaped (1 per cent.), (5) spherocytes, small, deeply staining corpuscles with regular circular outline (0.3 per cent.), in splenic blood about 5 per cent. About the third day polychromasia and basophilia are evident. Polychromatic normoblasts may occur late and at a late period the diameter of the red cells is increased. *Phagocytosis* by mononuclear and endothelial cells is best seen in the first twenty-four hours.

In the attack a marked *leukocytosis* (polynuclears, 90 per cent.) may be found, but later a condition of leukopenia exists, and at this time the following may be taken as a typical count: Large mononuclear 33, small mononuclear (lymphocytes) 6, polynuclear 61, eosinophile 0 per cent. Myelocytes and metamyelocytes appear late. The *splenic blood* shows shadow cells and spherocytes. Agglutinated red cells present or absent. Phagocytosis by cells of ill-definable types occurs and among the inclusions are (1) red cells, (2) very small mononuclear cells, (3) greenish masses, (4) chromatin masses (? platelets) and (5) melanin.

Treatment.—All effort should be directed from the outset to maintain the secretion of urine and to get the earliest warning of oliguria, for once

anuria is established the outlook is extremely grave. Every specimen of urine passed should be measured and estimates made of the specific gravity, color and amount of sediment. Blood counts and hemoglobin estimates from time to time give valuable information as to whether the hemoglobinuria is progressing.

From the onset as much fluid as possible, *e. g.*, dilute tea, barley water, etc., should be given by the mouth if the vomiting allows and the fluid should preferably be sucked through a tube. If fluid by the mouth cannot be given, 500 cc. of saline solution should be given by the bowel every few hours. The saline may also be given subcutaneously or best intravenously. If ketosis exists the administration of 500 cc. of glucose solution (5 per cent.) and sodium bicarbonate solution (2 per cent.) is advisable. By the mouth the glucose may be given flavored with lemon juice and the bicarbonate in dram doses or in the form of an alkaline drink (30 grains to the pint).

For *vomiting*, chloroform in the following mixture has many advocates: Chloroform 10, gum arabic 10, sugar 20, water 200. Of this 1 or 2 teaspoonfuls are given and repeated two or three times. A mustard plaster may suffice.

As regards the bowels, experience seems to show that it is advisable, in spite of the resulting depletion of water, to commence treatment with a calomel and saline purge or a glycerin enema. The use of hot water bottles, turpentine stupes, hot fomentations or dry cupping may reduce the pain in the loins but morphia may be required. For *hyperpyrexia*, tepid sponging should be employed for its antipyretic and sedative effect. Hot baths are also employed but require care and avoidance of syncope. *Bleeding* to the extent of 500 cc., followed if necessary by a saline injection, has been practised in severe cases with good result. But here as in many other forms of treatment advocated we have no clear evidence that the good result is due to the treatment.

Quinine.—Statistics based on about 1000 cases treated with and without quinine are in favor of "no quinine" 3 to 1, but on the other hand if parasites persist in the blood the physician should consider whether these are not responsible for a continuation of fever.

CHAPTER XIII

TRYPANOSOMIASIS

By Surgeon-General Sir DAVID BRUCE, K.C.B., F.R.S., D.Sc., F.R.C.P.

REVISED BY

GEORGE C. LOW, M.A., M.D., C.M., F.R.C.P.

Introduction.—Diseases caused by trypanosomes are found over a large area of the earth's surface, from South America, through Africa, Southern Europe, Persia to India, Burma, China, and the Philippines, and affect many kinds of animals, including man. These diseases are caused by the presence in the blood and body fluids of species of flagellated protozoa belonging to the genus *Trypanosoma*. A trypanosome consists of a single cell, and is a sinuous, worm-like creature, provided with a macronucleus and a micronucleus or blepharoplast, a long terminal flagellum, and a narrow fin-like membrane, continuous with the flagellum and running the whole length of the body. The end from which the flagellum protrudes is usually called the anterior; the other end, near which, as a rule, is situated the micronucleus, the posterior. When alive the parasite is extremely rapid in its movements, constantly dashing about and lashing the red blood corpuscles into motion with its flagellum; it moves equally well with either extremity in front. These trypanosomes give rise to an extreme variety of diseases, sometimes so acute as to cause death in a few days, at other times so chronic as to take several years to kill. Some of the species appear to live in the blood of their hosts without causing any perceptible disease, especially those which are parasitic to fish, frogs, and other cold-blooded animals. How the trypanosome damages its host is not very clearly known, but the probability is that it gives rise to small quantities of toxins and so causes, in some animals, chronic inflammatory processes, or in others extensive and rapid destruction of the blood corpuscles. However the damage is done, trypanosomiasis is extremely fatal in man and the domestic animals, such as the horse, dog, and ox. Large native populations in Central Africa have been swept away by this plague, and great tracts of country rendered uninhabitable for man and the domestic animals.

TRYPANOSOMA LEWISI

The Rat Trypanosome.—The earlier discoveries of trypanosomes in the blood of fish and frogs, dating from the year 1841, may be passed over. For about forty years little or no progress was made until Surgeon-Major T. R. Lewis,[1] F.R.S., Royal Army Medical Corps, made an

[1] *Quart. Jour. Micr. Sci.*, 1879, **19**, 109.

important observation by finding flagellated organisms in the blood of rats. Each organism consisted of a body portion and of an extension of it in the form of a gradually tapering, long flagellum. They were found in two species of rats -*Mus. decumanus* and *Mus. rufescens* -and in 29 per cent. of the animals examined. This rat trypanosome is distributed, broadly speaking, all over the world; and in Uganda, in Central Africa, numbers of the common field rat harbor it. The rat trypanosome does not appear to give rise to any symptoms of disease.

TRYPANOSOMA EVANSI

Surra.—This trypanosome was discovered in 1880 by Evans.[1] Surra is mainly an Indian disease, occurring in the Punjab and in Burma. It usually appears during the rainy season, and disappears gradually with the advent of cold, dry weather. The horse and mule are most susceptible, the dog coming next, and these three always succumb to the disease. The camel is supposed to live for three years after becoming infected, while the ox generally recovers after some five or six months. Rogers[2] states that surra is conveyed by species of tabanus, and other writers have stated that stomoxys also acts as an infection agent. Surra is very closely related to the next disease—nagana—and is considered by many to be identical.

TRYPANOSOMA BRUCEI[3]

Nagana or Tsetse-fly Disease.—As the writer had the good fortune to discover this species of trypanosome in 1894, perhaps a few words of personal experience will not come amiss. In 1894, when in Natal, South Africa, he was asked to go to Zululand to report on a disease which was causing severe loss among the native cattle. The native name of the disease was nagana. At this time no suspicion was entertained that nagana and the tsetse-fly disease were identical. The writer proceeded to Zululand and examined the affected cattle by ordinary bacteriological methods. The animals were emaciated with staring hair, some fever, and sometimes œdema of the subcutaneous tissues of the neck. Examination of the blood and organs for bacteria produced no result. Careful daily examinations of the blood were made and it was noted that a peculiar stained body, resembling an artistic dolphin, occurred from time to time among the red-blood corpuscles. It was thought at first that this was an accidental appearance due to the stain, but thinking that if the body was a parasite, it might show motion, specimens of fresh blood were examined and a very active body, wriggling and twisting about among the red-blood corpuscles was found. It was the first time the writer had seen a trypanosome, and, as then there was little or no literature on these parasites, it was difficult to know how to place it. A comparison with the description and drawing of the rat trypanosome in Lewis'

[1] *Report on Surra*, published by the Punjab Government, 1880.

[2] *Proc. Roy. Soc.*, March 14, 1901, vol. **68**.

[3] Bradford and Plimmer: "The *Trypanosoma Brucei*, the Organism found in Nagana or Tsetse-fly Disease, "*Quart. Jour. Micr. Sci.*, 1902, vol. **45**.

book[1] showed that it was a trypanosome. But there was no proof that the parasite was the cause of nagana; it occurred only in small numbers in the blood of the cattle, and the rat trypanosome lives as a harmless guest in healthy animals. Therefore, the blood of the infected cattle was inoculated into horses and dogs.[2] The disease in the horse and dog is much more acute than in the ox. In a few days the blood, especially of the dog, was found to be teeming with thousands of trypanosomes. It, therefore, began to appear probable that this parasite might be the cause of nagana. At that time there was no suspicion that this disease among the native cattle, in kraals situated many miles from the "Fly country," was the same disease as that known as the tsetse-fly disease. The work was being done on the summit of a mountain called Ubombo some 2000 feet above the surrounding country. The low country to the east of the mountain was infected with the tsetse-fly, and it was determined to take a few animals into this "Fly country" and see what the disease was like. After being there a fortnight the animals were brought back to the top of the mountain and examined. It was found that the blood of these animals affected with the tsetse-fly disease contained the same parasite as that found in nagana. In this way it was forced upon me that the two diseases, nagana and tsetse-fly, were one and the same.

Experiments were then made to find how the animals became infected, whether the fly was the carrier or a mere concomitant of the unhealthy district, and, if a carrier, if it was the only carrier of the disease. Horses taken down into the "Fly country" and not allowed to feed or drink there, took the disease. Bundles of grass and supplies of water brought from the most deadly parts of the "Fly country" to the top of Ubombo and there used as fodder for healthy horses failed to convey the disease. Tsetse-flies caught in the low country and kept in cages on the top of the mountain when fed on infected animals were capable of giving rise to the disease in healthy animals. The question then arose as to where the tsetse-flies obtained the trypanosomes. The flies lived among the wild animals, such as buffaloes, and species of antelopes, and fed on them. It seemed that, in all probability, the reservoir of the disease was in the wild animals. Therefore all the different species of wild animals obtainable were investigated by the injection of their blood into healthy susceptible animals, and by examination of the blood itself. It was discovered that many of the wild animals harbored this trypanosome in their blood. The parasites were never numerous, and the wild animals did not seem to be affected by them; they showed no signs or symptoms of the disease, and it therefore appeared probable that the trypanosomes lived in their blood as harmless guests, as the trypanosome of the rat lives in the blood of that animal.

Nagana affects a large variety of species of animals. With the exception of the baboon, it is fatal to monkeys, horses, mules, donkeys, cattle, dogs, cats, rabbits, guinea-pigs, rats, mice, and other animals.

[1] Lewis, T. B.: *Physiological and Pathological Researches*, 1888.

[2] Bruce, D.: *Preliminary Report on the Tsetse-fly Disease or Nagana in Zululand*, Durban, Natal, 1895, *Further Report*, printed for the Royal Society by Harrison & Sons, London, 1896; *Appendix to Further Report*, Harrison & Sons, 1903.

TRYPANOSOMA GAMBIENSE AND TRYPANOSOMA RHODESIENSE. HUMAN TRYPANOSOMIASIS. SLEEPING SICKNESS.

Historical.—The *Trypanosoma gambiense* was first described by the late Dr. J. E. Dutton, in 1901, in a patient of Forde[1] on the Gambia. The latter observer noted the parasites and showed them to Dutton[2] who recognized them as trypanosomes and named then *T. gambiense*.

This discovery awakened great interest, and Dutton and Todd were sent to Senegambia to make further investigations. They examined 1043 natives in the Gambia, and found the parasite in 6 cases only. They sum up their report by saying that they believe the disease, as it occurs in natives, to be a peculiarly mild one, and they suggest the possibility that the natives in this disease may bear the same relation to Europeans as does the wild game of Central Africa to domestic animals in the tsetse-fly disease.[3]

In 1903, Baker[4] noted the presence of trypanosomes in 3 cases in the blood of man in Entebbe, Uganda. Shortly before this Castellani,[5] a member of the Commission sent to Uganda by the Royal Society, London, for the purpose of investigating sleeping sickness, had observed these hematozoa in the cerebrospinal fluid of 5 cases of sleeping sickness, and in 1 of these he had also seen them in the blood. This was the first time trypanosomes had been seen in the blood of recognized cases of sleeping sickness. When the writer arrived in Uganda, on March 16, 1903, for the purpose of continuing the investigation, Castellani described his findings, and consented to stay longer, in order that this particular point might be pursued. He remained in Entebbe for three weeks, and during this time 22 cases of sleeping sickness were examined, trypanosomes being found in 15, or about 70 per cent.

From this time the history of *Trypanosoma gambiense* became merged in that of sleeping sickness and it was soon proved that trypanosoma fever was but the first stage of sleeping sickness. Later Stephens and Fanthan described, under the name of *Trypanosoma rhodesiense*, the trypanosome which is found in cases of human trypanosomiasis in Nyasaland and Rhodesia.

There is considerable difference of opinion as to the systematic position of the human trypanosomes. Kinghorn and Yorke found *T. rhodesiense* in 16 per cent. of the game in the Luangwa Valley, Northern Rhodesia, and Bruce and his fellow workers confirmed this in Nyasaland. Kleine, Eckhardt, Tante and Fischer, however, though agreeing that this trypanosome is closely related to *T. rhodesiense*, hold that the parasites are not identical. Tante, by human experiments has produced some confirmation of this. More recently Duke[6] has considered the possibility of all

[1] *Jour. Trop. Med.*, September 1, 1902.

[2] *Thompson-Yates Laboratory Reports*, 1902, **4**, 11.

[3] Dutton and Todd: *First Report of the Expedition to Senegambia*, Liverpool School of Tropical Medicine, 1902, Memoir XI.

[4] *British Med. Jour.*, 1903, i, 1245.

[5] "Presence of Trypanosoma in Sleeping Sickness," *Royal Society Reports of the Sleeping Sickness Commission*, 1903. Harrison & Sons, London.

[6] *Parasitology*, 1921, **13**, 352–297.

the polymorphic mammalian strains of African trypanosomes being one. If this species be called *T. brucei*, then *T. gambiense*, *T. rhodesiense* and *T. nigeriense* are to be regarded as particular strains of *T. brucei* which have become, after sojourn in other hosts, more or less adapted to life in the blood of man. Finally Brumpt comes to the conclusion that *T. rhodesiense* is a good species. For the purposes of this article we shall consider *T. gambiense* and *T. rhodesiense* as distinct and as good species.

Human Trypanosomiasis or Sleeping Sickness.—Human trypanosomiasis or sleeping sickness, known for more than a hundred years on the West Coast of Africa, attracted a good deal of interest and curiosity on account of the peculiar symptoms of lethargy and which gave rise to the name of sleeping sickness. The disease was found to lose its power of spreading from man to man upon removal to a non-endemic area. Different theories were held as to its causation, but all these fell to the ground when it was discovered that the trypanosome was the real cause.

Etiology.—*Geographical Distribution.*—The disease was first reported by Atkins in 1734 on the West Coast of Africa. On the West Coast of Africa it extends from Senegal in the North to San Paola de Loanda in the South, and in addition spreads into the hinterlands of the different colonies. Large areas of the Belgian Congo are affected and the disease spreads from here across the continent to Uganda. A form of the disease has appeared, or at least has been recognized, in Nyasaland and Rhodesia. It varies in intensity in these different parts and seems to have largely died out on the West Coast or at least become feebly endemic. In Uganda and parts of the Congo it has raged in epidemic form and has killed large numbers of the population. In other parts of the world sleeping sickness does not occur. A South American form of trypanosomiasis has been discovered, but this is in no way similar to the African form.

Race.—For a long time it was considered that the disease was confined to negroes. Unhappily, this is not so; Europeans, natives of Persia and India, and other parts are equally liable to it.

Occupation.—Occupations leading people to spend their time in areas where *Glossina palpalis* occurs are dangerous. Hence, fishermen, canoemen and the inhabitants of places like lake shores and river banks in the endemic area are prone to suffer. Sex, age, food, health or ill-health have no effect; if the trypanosome is introduced under the skin of the youngest or the healthiest there is no reason to believe that it does not multiply.

Months and Seasons.—As the climate in Central Africa is much the same all the year around it does not appear that the disease is more prevalent at one season than at another.

Description of the Causal Agents—the Trypanosoma Gambiense and Trypanosoma Rhodesiense.—The trypanosomes may be demonstrated in the blood, in the cerebrospinal fluid, or in the lymph from lymphatic glands.

1. *In the Blood.*—As a rule the parasites are very scanty here, so if not found in ordinary blood films it is necessary to take 10 c.c. of blood in a test-tube with a small quantity of sodium citrate solution, and centrifuge this for fifteen minutes. After this the clear liquid is pipetted off and

again centrifuged and then the sediment is examined. For bringing out the various details of the parasites in films any of the various modifications of the Romanowsky technique may be employed. Leishman's and Giemsa's methods are especially applicable. The macronucleus appears red, the micronucleus black, the flagellum red, and the basophile granules black, while the protoplasm of the parasite is colored blue.

Fig. 51 represents the trypanosomes in the blood, magnified 2000 diameters, and shows the macronucleus in the centre of the body, the micronucleus at the posterior end; the flagellum taking its origin from the micronucleus, and, running along the margin of the undulating membrane, becomes free at the anterior extremity. A large vacuole is seen near the micronucleus and dots of chromatin are scattered through the

Fig. 51

Trypanosomes (T. gambiense) from the blood in sleeping sickness. × 2000.

protoplasm. Some writers profess to be able to recognize the various species of trypanosomes by their shape and general appearance, but as a matter of fact it is very difficult to distinguish between such trypanosomes as *T. evansi*, *T. brucei*, and *T. gambiense* by microscopic examination alone. The chief morphological distinction between *T. gambiense* and *T. rhodesiense* is the occurrence of posterior nuclear forms (nucleus close to centrosome or even behind it) in the latter when inoculated into rats.

2. *In the Cerebrospinal Fluid.*—In the earlier stages of human trypansomiasis the trypanosomes are seldom, if ever, found in the cerebrospinal fluid. It is only when the symptoms of sleeping sickness have appeared that they are found with any frequency. Ten to 15 c.c. of the cerebrospinal fluid are allowed to flow into a test-tube. If any blood

escapes with the cerebrospinal fluid the specimen ought to be rejected. The fluid is then centrifuged for twenty minutes to one-half hour, and the sediment examined under a low power. The trypanosomes are seen very readily.

3. *In Enlarged Lymphatic Glands.*—One of the earliest manifestations of trypanosomiasis is an enlargement of the lymphatic glands; all of these are enlarged. The trypanosomes can be demonstrated with great ease in the swollen lymphatic glands, where they seem to be in much greater numbers than in the blood or cerebrospinal fluid. Greig found that it was only necessary to draw off a drop of fluid by means of a small hypodermic syringe from one of the enlarged cervical glands and to place this fluid under the microscope to find the trypanosomes at once or in a comparatively short time.

In What Tissues can the Trypanosoma Gambiense and T. Rhodesiense be Found?—The trypanosomes are found in much greater numbers in the juice of the glands than in any other of the fluids of the body. From the glands they evidently pass in small numbers into the general circulation. In the first stages of the disease the trypanosomes are not found in the cerebrospinal fluid. In an examination of many apparently healthy natives who had trypanosomes in their blood, trypanosomes were not found in a single case by lumbar puncture. In the later stage, however, when the symptoms of sleeping sickness supervene, the trypanosomes can, as a rule, be readily found in this fluid in every case of the disease.

Mode of Reproduction of the Trypanosoma Gambiense and T. Rhodesiense.—As far as is known at present these trypanosomes only reproduce themselves within the human organism by longitudinal division. Other modes of reproduction have been described, but these are not sufficiently definite to warrant acceptance. The number of trypanosomes varies greatly from time to time in the blood and fluids. Huge numbers must perish at times and their dead bodies become dissolved in the blood plasma. It is supposed by some that these dead trypanosomes contain a small quantity of toxin which is thus set free in the blood and gives rise to the proliferation of the lymphatic elements, and to the chronic conditions afterward found in the brain and tissues.

Life History of Trypanosoma Gambiense and T. Rhodesiense Outside the Body.—It is evident that as the parasites are only found in the blood and lymphatic fluids of the body, they can only leave it on the escape of these fluids. There is no evidence that the trypanosome escapes from the body by the intestinal or urinary tracts or by the sweat, salivary, or other secretions. When an animal dies of the disease all the parasites disappear rapidly from the tissues on account of commencing putrefaction. If blood is drawn off during life and kept aseptic it only retains its virulence for four days. Blood dried on threads sometimes retains its infectivity for twenty-four hours, but at the end of forty-eight hours it is inert. If exposed to a temperature of 40° to 44° C. it is slowly killed; 45° C. is rapidly fatal. Trypanosomes, like some bacteria, can be frozen at the temperature of liquid air (—191° C.) for a quarter of an hour and still retain their vitality. Novy and MacNeal showed that trypanosomes can be cultivated and live and develop on artificial media outside the

body. The culture medium used was ordinary nutrient agar to which defibrinated rabbits' blood was added. They first succeeded in growing the rat trypanosome in 1903. Later they succeeded in cultivating *Trypanosoma brucei* outside the body. These cultures are, however, by no means so readily obtained as in the case of the rat trypanosome. In this way *T. brucei* has been grown artificially through twenty-three generations. *T. gambiense* and *T. rhodesiense* have also been cultivated but with greater difficulty. It is to be hoped that the cultivation of the various trypanosomes will assist in the identification of species, as their classification is rather chaotic. The common way in Nature for the trypanosomes to leave the body is by the agency of biting flies. The blood along with the trypanosomes is sucked into the stomach of the tsetse-fly. Up to forty-six hours one can see living trypanosomes and red-blood corpuscles in the proboscis, and it is possible, especially if the fly is interrupted in its feeding that it may convey the parasites direct to another animal at this time. Afterward it becomes non-infectious and remains so up to the eighteenth day or longer after feeding, when it again becomes infectious. Miss Robertson describes the cycle of development that takes place during this time. If such a fly be dissected, its gut will be found to be swarming with trypanosomes and forms will also be met with in the salivary glands. It would seem that this latter occurrence is necessary before infection of a new host can take place. Miss Robertson believes that the trypanosomes reach the salivary glands by passing up the alimentary tract until they reach the openings of the salivary ducts; they then pass down these to the glands. There does not appear to be a general body infection as is the case with the sporozoites of malaria. Only a small percentage of flies (5 per cent. or so) became infected after sucking the blood of suitable infected animals. Temperature and other conditions influence this to a marked degree.

How do the Trypanosomes Gain Entrance to the Human Organism?— The answer to this question is by means of the bites of infected *Glossina palpalis* and *Glossina morsitans*. Full descriptions of the tsetse-flies are given in Austen's[1] monograph, from which the accompanying Fig. 52 is taken, showing *Glossina palpalis* with artificially outspread wings.

In Uganda, the experiments made to find out if this fly (*Glossina palpalis*) was capable of carrying infection from the affected to the healthy were as follows: Tsetse-flies contained in small muslin-sided cages were fed on sleeping sickness patients and then, after a certain time had elapsed, on healthy monkeys. Such flies fed on healthy monkeys, were capable of transmitting the disease. But this was not the only proof that these flies could carry the infective agent. On the lake shore there was a large native population among whom we had found about one-third to be harboring trypanosomes in their blood. The tsetse-flies caught on this lake shore, brought to the laboratory in cages and placed straightway on healthy monkeys, gave them the disease. The white man runs much less danger than the half-naked native. He is clothed, as a rule, from head to foot, and resents the presence of a biting fly;

[1] *Monograph of the Tsetse-flies*, Longmans, Green & Co., London.

whereas the natives lie almost naked in the shade of the dense woods and are little affected by the presence of the tsetse-flies.

Are Other Species of Tsetse-flies besides Glossina Palpalis Capable of Carrying the Infection?—Probably this question must be answered in the affirmative, as Wiggins, experimenting in British East Africa with *Trypanosoma gambiense* and species of tsetse-flies other than *palpalis*, succeeded in infecting healthy from infected animals, and Greig and Gray in Uganda found that *Glossina palpalis* could convey the trypanosoma of a disease, probably nagana, which occurred among cattle, as well as that of sleeping sickness. The carrier of the trypanosomiasis which occurs in Rhodesia and Nyasaland is the *Glossina morsitans*, and in experimental work this fly has also been shown to be capable of trans-

Fig. 52

Glossina palpalis, Rob. (× 31.)

mitting *T. gambiense*. Nagana and some of the other animal trypanosomes seem to be capable of developing in both. Another tsetse, *G. fusca*, may also have to be incriminated. As far as our present knowledge goes all tsetse-flies should be viewed with suspicion.

Do Flies Other than the Glossina Carry the Infection?—The answer to this is in the negative. Nuttall states that he tried for a long time in England to convey the *T. brucei* by means of the genus of biting flies called *Stomoxys*. In no case did he succeed. Greig in Uganda tried the same experiment and failed. In regard to the *T. brucei* and nagana, there can be little doubt that it is carried by *Glossina* alone, and the distribution of nagana corresponds with the distribution of the tsetse-fly. So in regard to human trypanosomiasis in Uganda, if the *T. gambiense* is only carried by the *Glossina* then the distribution of the fly and the dis-

ease should correspond. Collections of all sorts of biting flies were made from all parts of Uganda, and the distribution of sleeping sickness was carefully inquired into. In a few months several hundred collections of biting flies were examined. These were divided into two categories, those containing tsetse-flies and those containing other kinds of biting flies but no tsetse. Two maps were taken, one to represent the distribution of *Glossina palpalis*, the other sleeping sickness. When these maps were completed it was found that the distribution of *Glossina palpalis* and sleeping sickness coincided, and therefore we came to the conclusion that human trypanosomiasis is conveyed from the sick to the healthy by the *Glossina palpalis* and by it alone. Confirmation has come from many different parts of Africa. With the exception of Rhodesia and Nyasaland, where *G. morsitans* acts as the carrier, the rule may be laid down that where sleeping sickness exists so also does *G. palpalis*, the fly being necessary for the transmission of the *T. gambiense* from person to person.

This tsetse-fly is only found on the shore of the lake where there is forest. This forest is thick jungle with high trees and dense undergrowth. The fly is never found on open, sandy beaches backed by grass plains, even although there may be some scrub near the water's edge. It was never found in the grass of the grassy plains. It was not found in banana plantations, and not at any time far from the lake shore. Most of the rivers in Uganda are mere swamps, and up these valleys the fly does not penetrate. The fly is found along the Nile almost as far north as Gondokoro on the border of the Sudan. It also occurs around Albert Nyanza and is present in the sleeping sickness areas of the Congo and other parts.

Animals to Which Trypanosoma Gambiense and T. Rhodesiense are Pathogenic.—*T. gambiense* and *T. rhodesiense*, like *T. brucei*, are pathogenic to many species of animals. It is curious that *T. gambiense* and *T. rhodesiense* should include man in their attack, as well as the other animals, whereas *T. brucei*, although, as a rule, much more rapidly fatal and acute in the lower animals, so far as we know, does not attack man unless some cases in Rhodesia have been due to this parasite. A supposed case of nagana infection in a laboratory in Italy lends support to such an idea.

Special Pathology.—The body may be nourished, or extremely emaciated. The effect of the long chronic toxemia renders the heart muscle flabby and the liver fatty. The lungs and kidneys present nothing abnormal, except the congestion incident to a failing circulation. In a malarious region, the spleen is generally enlarged and pigmented. Except for the constant general enlargement of the lymphatic glands, there is nothing in the naked-eye appearances to proclaim human trypanosomiasis. The lymphatic glands, both superficial and deep, are enlarged. The superficial usually vary in size from a pea to a large bean, and the deep are somewhat larger. Sometimes they increase very much in size, and on section are caseous or contain collections of pus. This is probably due to some terminal bacterial invasion and not to the trypanosomes. In the brain the picture is fairly regular. The convolutions on the surface of the brain are flattened, and the sulci with opaque-looking subarachnoid

fluid, giving a ground-glass appearance. The vessels on the surface are injected. On section the brain appears normal, but the lateral ventricles are dilated and contain an excess of fluid. A certain percentage of the cases present much more acute signs of disease. These are the cases in which a terminal bacterial infection has taken place, and the brain may then present the appearances of acute or purulent meningitis.

Histology.—It is to Mott we owe our knowledge of the pathological histology of sleeping sickness. He states that a definite characteristic appearance of meningo-encephalomyelitis is found. Throughout the whole central system, but especially in the medulla and at the base of the brain, sections show the pia-arachnoid to be infiltrated with mononuclear leukocytes; the inflammation can be traced along the bloodvessels and septa into the substance of the nervous system. The perivascular lymphatics around both large and small vessels are crowded with these lymphocytes. Fig. 53 is taken from his paper, and shows this collection

FIG. 53

of cells in the perivascular spaces. Similar accumulations are found in the other organs. There is an increase of the mononuclear cells in the blood and the lymphatic glands are enlarged and show a proliferation of their cells. Throughout the body, and especially in those tissues and organs rich in lymphatics, such as the intestine, this proliferation and accumulation can be seen. Human trypanosomiasis is essentially a disease of the lymphatic system, and the irritation and proliferation of the lymphocytes are probably due to a toxin secreted by, or contained in, the bodies of the trypanosomes. The characteristic symptoms are no doubt due to the accumulation of these mononuclear cells in the perivascular spaces of the brain, compressing the arteries and so interfering with the normal nutrition of the brain cells. Stevenson has shown that the trypanosomes may be found outside the vessels in the tissues themselves. The progressive weakness, the tremulous condition of the muscles, the feeble, rapid pulse, the weak voice, and uncertain gait, the rise of tem-

perature, would be accounted for by this obstruction or interference with the circulation, giving rise to degenerative changes in the nerve cells, and proliferation of the neuroglia.

Terminal Bacterial Invasion.—In certain instances bacterial infections take place in the late stages and quickly carry off the debilitated patient. Streptococci, pneumococci, colon bacilli, and other germs have been described. Pneumonia and purulent meningitis sometimes occur.

Symptoms.—*Effect of Trypanosoma Gambiense on Man—First Stage—Trypanosomiasis.*—When the *T. gambiense* gains entrance into the human organism it begins to multiply and appears in the blood. How long before it appears in the general circulation is unknown, but in the monkey it usually appears about twenty days after inoculation. The course of the disease is so slow and insidious that months and even years may elapse before any marked signs appear. The first stage, when the trypanosomes are found in the blood but not in the cerebrospinal fluid, may be of a very variable duration. If one may put this into definite figures, it may be said that this so-called stage of trypanosoma fever, this first stage of human trypanosomiasis, may last from three months to three years or more. During this time the native is going about and feels perfectly fit and strong. But there is one outward mark which proclaims the disease and that is the presence of enlarged lymphatic glands. This is a disputed point, but in most cases certainly this enlargement of the lymphatic glands is a constant and early feature. It is not that enlargement of the inguinal or femoral glands should be taken as a sign of human trypanosomiasis; there must be a polyadenitis, and, as a matter of routine, the postcervical glands should be examined first. Every case of sleeping sickness examined by us in Uganda showed this glandular enlargement, and the trypanosomes are readily demonstrated on examining the gland juice. Later it was found that the early cases of trypanosomiasis, the so-called trypanosoma or Gambia fever, also, in most cases, presented enlargement of the lymphatic glands, and in these active trypanosomes could readily be found. The natives are alive to the fact that when the glands in the neck enlarge, they will, sooner or later, pass into the stage of sleeping sickness. This enlargement of the cervical glands may be used to gauge the incidence of the disease in a sleeping sickness area. Whether there is any other symptom which can be depended upon to point to the first stage of this disease is a question which, must be answered in the negative. Some writers state that there is irregular fever from time to time, but the charts of the men under observation in Uganda showed a normal temperature for several months. The first stage may be dismissed by saying that the blood and lymphatics contain the trypanosomes, and that there is a general enlargement of the lymphatic glands. In Europeans this quiescent stage is not so marked. In a short time after inoculation definite symptoms appear, among which are irregular fever and in some cases a circinate erythematous eruption over the body. The spleen also becomes enlarged and eye lesions have been noted.

Second Stage—Sleeping Sickness.—Naturally, in a disease so insidious it is impossible to say with absolute accuracy when the first stage merges into the second. But a time comes when a slight change in the patient's

demeanor becomes evident; he is less inclined to exert himself and lies about more during the day. The expression of the face becomes sad, heavy, dull-eyed, and apathetic, as shown in Fig. 54. The body is well nourished, and this is the rule, even up to the time of death, if the patients are well nursed and fed. Complaints of headache or indefinite pains in other parts of the body are often made. The pulse is rapid, shallow and weak, and the heart-sounds faint and distant. The breathing usually presents nothing abnormal. The lymphatic glands are generally enlarged, and vary from the size of a pea to that of a bean. There is nothing abnormal about the skin; it may be at times harsh and rough, but usually is

FIG. 54

Sleeping sickness. Second stage.

smooth and sleek, and any eruption is the exception. The circinate erythema cannot be detected on the native skin. The gait is weak, uncertain, and shuffling. There is little strength in the hand grip, and the hands when held out are tremulous. Tremors of the tongue are, as a rule, well-marked. The voice is weak, indistinct, and monotonous. At this time the temperature is usually irregular, often normal in the morning, and rising to 101° or 102° F. in the evenings. During this time the patients in hospital to the casual observer may show little or no signs of disease. The symptoms gradually increase until after weeks or months the patient is unable to walk, speak, or feed himself. He is then confined to his bed, lying in an absolutely lethargic condition. It is at this time

that the sick are often neglected by their friends and become much emaciated. The urine and feces are passed involuntarily. During the last two or three weeks the temperature becomes subnormal, and the patient dies in coma. Fig. 55, represents a case of the emaciated type a few days before death.

Nervous System.—The dull, heavy, listless, expressionless, emotionless physiognomy is a marked feature. Often when a patient is being examined he stares at a fixed point in a vacant way with eyes wide open. The intelligence and memory seem, as a rule, to remain fairly good. Sometimes cases showing mental excitement are seen. In regard to sleep the usual history is that the patients sleep well at night and a good deal during the day. The condition, however, can hardly be called sleep. It is rather a vacant, day-dreaming, apathetic condition in which the patient remains for hours, often with eyes open, staring unmeaningly at the wall. They can easily be roused by touching or speaking to them. The speech is peculiar, weak, slow, tremulous, and indistinct, sometimes faint and

FIG. 55

Sleeping sickness. Shortly before death.

high-pitched, like a whimpering child. When asked a question some little time elapses before the patient answers; he gives, as it were, a sigh, gathers his wits together, and answers with an evident effort. There is nothing, as a rule, noteworthy about the eyes. There is frequently marked tremor of the tongue, lips, and hands, but the tongue alone may be affected. Sensibility to touch and temperature is normal, and the muscular sense is little impaired. Delayed sensations to pain (Kerandel's sign) may be found. In regard to the reflexes, as a rule there is no abnormality. Sometimes, in the early stages, the knee-, elbow,- and wrist-jerks are increased; but in advanced cases the knee-jerks are often diminished and ankle-clonus is in rare cases present to a slight extent.

Cerebrospinal Fluid.—As Greig and Gray have shown, the cells in the cerebrospinal fluid are mononuclear and increased in number from 23 in the early stages to 700 in the fully developed disease. Broden and Rodhain have shown that the cell content of the spinal fluid may be looked upon as an index of the extent of cerebrospinal involvement, thus serving as a diagnostic criterion and a therapeutic guide. The first abnormality

in the cerebrospinal stage of the disease is an increase in the lymphocytes, followed, in the later stages, by the appearance of medium-sized mononuclear cells and so-called mulberry cells or large vacuolated mononuclear cells (cellules en mûre). In very advanced cases extremely large vacuolated cells, polymorphonuclear cells with eosinophile granules, and cells apparently from the meninges, may be present.

Alimentary System.—The appetite is usually good, even in fairly advanced cases. There is, as a rule, no enlargement of the liver; the spleen is palpable. The bowels tend to be constipated.

Circulatory System.—The heart and pulse tend to become affected early. The heart sounds are weak but regular, and there is, in the great majority of cases, no bruit. The pulse is usually accelerated from about 90 to 100 or over with a low tension, a small size, easily compressible and regular rhythm.

Respiratory System.—Pneumonia seems to supervene more frequently in sleeping sickness cases than among the healthy.

Urinary System.—This shows, as a rule, nothing noteworthy.

Cutaneous System.—Sometimes the skin is harsh and rough, and the papillæ prominent, but in the great majority of cases there is nothing abnormal. In some cases œdematous swellings are seen over the shins and under the eyes.

Lymphatic System.—In every case the superficial lymphatic glands are slightly enlarged, varying, as a rule, from the size of a pea to a bean. They are fairly soft and painless, but in a few cases in the last stages they become inflamed, tender, and break down. This is probably due to a terminal bacterial invasion. This polyadenitis is very characteristic and is only found among natives inhabiting the sleeping sickness area. It may be accepted as the most marked sign of the disease.

Hemopoietic System.—In the early stages the blood may be little altered; later varying degrees of anemia are found. In a certain proportion of cases a polycythemia is seen in the terminal stages with a rise in the percentage of hemoglobin and specific gravity. The cause of this is not clear. The leukocytes are normal or diminished. Just before death a terminal polymorphonuclear leukocytosis, coincident with the final fall of temperature is often noted. The mononuclear cells are relatively increased, the total number of large mononuclears and lymphocytes, generally exceeding 40 per cent. of the total. Varying degrees of eosinophilia, generally due to helminthiasis, are also found.

Temperature Curve.—There is nothing very marked about this in human trypanosomiasis. In the early stage, when the trypanosomes are found in the blood and before symptoms of sleeping sickness appear, the temperature may remain normal. In Europeans an irregular remitting temperature is common. When symptoms of sleeping sickness appear, the temperature, as a rule, becomes irregular, rising to 101° F. or 102° F. in the evening and sinking to normal or slightly below normal in the morning. Other cases occur with the temperature fairly normal throughout the disease, although there is always a certain irregularity. High temperatures may be said never to occur—103° F. being exceptional, and probably due to an attack of malaria. There is one characteristic

which is fairly constant: about a fortnight before death the temperature runs rapidly down to 94°, 93°, or even 92° F., and remains so until death. When the temperature becomes subnormal morning and evening, the patient will probably die within a fortnight.

Diagnosis.—It is no easy matter to diagnose human trypanosomiasis in the early stages. All irregular fevers resistant to quinine and occurring in people who have lived in a trypanosomiasis area should be viewed with suspicion. In natives there may be no fever and this makes the diagnosis even more difficult. The pulse should be examined carefully, as increased rate and low tension are suggestive. The examination of the blood will show a relative mononuclear leukocytosis, which will help to exclude other diseases; and a drop of gland juice, removed by a hypodermic needle from a cervical gland, should show the trypanosomes and so settle the diagnosis. In more advanced cases the peculiar apathetic physiognomy, the pulse, the temperature curve, the tremors of the tongue and hands, the peculiar speech and weak shuffling gait, form a picture which cannot be mistaken for any other disease. But the one unmistakable finding is the presence of the trypanosome in the lymphatic glands, blood, or cerebrospinal fluid, and no one should rest content with a diagnosis which does not include the demonstration of the parasite.

Prognosis.—Every patient with human trypanosomiasis who shows symptoms of sleeping sickness dies sooner or later, if untreated. It is an absolutely fatal disease. The question has arisen as to whether any of the natives with trypanosomes in their blood are able to kill off the parasite before organic changes in the tissues have been set up and so establish an immunity. This question can be answered in the affirmative. Greig and Gray state: "In following the after-history of cases of trypanosoma fever we have arrived at these conclusions: (1) That many of them terminate fatally as sleeping sickness cases, which may be regarded as the usual mode of termination; (2) that a certain number die of intercurrent affections, *e. g.*, pneumonia; (3) that a certain proportion remain well for long periods, indicating that a tolerance toward the parasite has been obtained. It may be said that some of the cases may become in time sufficiently immune to destroy the parasite." The prognosis of human trypanosomiasis at the present day, with improved methods of treatment, is more hopeful. Taken early a certain number of recoveries may be anticipated, and a good number of Europeans, who have had trypanosomiasis, are well after the lapse of five years or more after the original infection. If some patients have recovered there is always hope for others, especially in view of improved methods of treatment. Once signs of sleeping sickness develop however, the prognosis becomes much more serious. In natives a very great proportion of the trypanosomiasis cases pass into the stage of sleeping sickness and die. The form of the disease in Rhodesia and Nyasaland is extremely virulent and kills very quickly, generally in a few months. A few have recovered, however, after prolonged treatment.

Treatment.—Arsenic in some form or other has more influence on the trypanosome than any other drug. Horses, donkeys, and cattle suffering from nagana received 12 to 20 gr. of arsenic daily. The result was that

in a few days the parasite disappeared altogether from the blood and remained out of it for a time—from one to five or six months. In every case, sooner or later, the hematozoa crept back into the blood, increased in numbers, and finally killed the animal. In no case was a cure effected. In the most successful case death was delayed for nearly a year. In human trypanosomiasis arsenic, atoxyl, soamin, arsenophenyl, salvarsan, mercury, antimony, and various anilin and other dyes have been tried. Some of these drugs, when given in doses sufficiently large to kill the parasites, produce toxic symptoms, such as optic neuritis and atrophy, and must be used with caution. Repeated intravenous doses of tartar emetic (gr. $\frac{1}{2}$ to $2\frac{1}{2}$, gm. 0.032 to 0.15) have done good in certain cases. Such treatment, combined with moderate doses of atoxyl (gr. 3 to 4, gm. 0.2 to 0.25) given bi-weekly until a total of 100 grains has been reached has been the standard for some years. Recently two new drugs have been introduced, viz., Bayer "205" and Tryparsamide. The composition of the former is not definitely known. It is related to trypan blue and, according to French chemists who have recently analyzed it, is a complicated compound of urea. It does not contain arsenic or antimony. The drug is given intravenously in 1-gm. doses every week for ten weeks, until a total of 10 gm. in all has been taken.[1] [2] Kleine proposes a course of 5 gm., as a total, but it is questionable if this is safe, as relapses may occur after 4 gm. The action seems to be immediate and in favorable early cases all symptoms quickly disappear and the patient recovers. One disadvantage of the drug is that it produces albumin and casts in the urine in all the cases. This disappears, however, in time when the course is finished, and as far as one can judge, no permanent damage appears to be left behind in the kidneys. Skin lesions also occur.

Tryparsamide is the sodium salt of N. phenylglycine amido-p-arsenic acid and is best administered intravenously in a 20 to 30 per cent. solution (it can be given subcutaneously or intramuscularly). Dr. Louise Pearce, of the Rockefeller Institute who has tried this drug in natives of the Congo, speaks highly of it. She has given us the details of dosage and administration as follows: *Early cases*, with normal cerebrospinal fluid, a total amount of 20 to 30 gm. *Advanced cases*, a total amount of 40 to 60 gm. in two to three courses of 20 to 30 gm. separated by intervals of two to three months. The individual doses are 2 to 3 gm. (adult). In advanced cases with markedly altered spinal fluids and depleted physical condition, it is advisable to begin with a few doses of 2 and 2.5 gm. before giving 3 gm. doses.

The only untoward effect observed in the use of tryparsamide in trypanosomiasis has been a few instances of visual disturbance. Most of these have been transitory but a few have resulted in permanent disability. It is thought that this effect is related to the resolution and healing of lesions of the optic structures in certain patients as well as to a toxic effect upon the nerve itself.

A good number of Dr. Pearce's original cases seem to have recovered and

[1] Low, G. C. and Manson-Bahr, P.: The Treatment of Human Trypanosomiasis; *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1923, **16**, 339.

[2] Low, G. C.: A Second Series of Cases of Human Trypanosomiasis Treated by Bayer "205" with an Account of the After Histories of Some of the First Series, *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1924, **17**, 464.

others treated by Dr. G. C. Low with "205" have certainly done so. At the present moment then these two drugs are the best we have for the treatment of trypanosomiasis. Whichever drug treatment is adopted it is of the utmost importance to build up the patient's strength in every way possible. It is this part of the treatment that probably accounts for the whites doing so much better than natives.

Prophylaxis.—There are three factors to be considered: The human host, the parasite, and the tsetse-fly. If this were a disease affecting a species of the lower animals it is evident that the slaughter of all those with parasites in their blood would in all probability nip an epidemic in the bud. But we are dealing with man. The disease spreads only by means of the tsetse-fly, and in its absence there can be no infection. Is it possible to destroy these flies? They are present in great numbers all around lake shores, where there is dense forest. It has been found that cutting down the bush and clearing the land will get rid of these flies, and much has been done in this line in Uganda, with excellent results. When one comes to Rhodesia and Nyasaland, where *G. morsitans* is concerned, it is quite a different matter, because the distribution of this fly is much more widespread, and its destruction or diminution would seem to be impossible. When once the bionomics of the tsetse-flies are better known some means may be found for destroying their pupæ or attacking the flies in their adult stage. The real crux of the situation as regards prophylaxis lies in the question of the animal or natural carriers of the parasites. When it was discovered in Uganda that the disease was limited to the *Glossina palpalis* and infected areas of the lake shore, the population was moved back into the hinterland away from the fly and the spread of the disease was stopped. It was thought that infected flies would disappear after some years and that then the people could safely return. This was found not to be the case, infected flies still existing even after long periods of time. Finally it was discovered that the different wild buck inhabiting the infected zone were harboring the parasites, though showing no sign of the disease, and thus were infecting the flies. Kinghorn and Yorke showed that the same thing holds good in Rhodesia, the wild game acting as the carriers of *T. rhodesiense*. The question therefore arises, Is it possible to destroy the game and so prevent the tsetse-flies becoming infected? The flies without the infection are of course harmless. Before any steps are taken in this direction more experimental work is urgently required,

Movements of natives from sleeping sickness areas into non-infected areas must be strictly watched. The opening up of different parts of Africa by railways, with increased facilities for travel, has been largely responsible for the spread of the disease into parts where it was previously unknown. If it is necessary to have towns or settlements near river banks or lake shores in palpalis areas much can be done to render these safe by cutting down the jungle in the vicinity and cultivating the ground. Landing places for canoes and paths through the zone must be made broad and kept cleared of all bush. As regards personal prophylaxis, there must always be a risk in going into tsetse-fly infected areas. In such cases as much as possible of the face, neck, and hands should be covered, so as to get bitten as little as possible.

CHAPTER XIV

THE LEISHMANIASES

By BOWMAN CORNING CROWELL, M.D.

Introduction.—History.—The disease Kala-azar has been known in India as far back as 1869, when it was called by the name "Kala-azar" by the natives of the Gâro hills in Assam. Its incidence, its tendency to spread and its tendency to become epidemic were noted in various parts of India. Various theories as to its cause were held up until May, 1903, when Sir William B. Leishman published his finding of an organism, since known as *Leishmania donovani*, in smears from the spleen of a case of splenomegaly that came from Dum-Dum, in Bengal. In July, 1903, Donovan observed the same organism in blood obtained by puncture of the spleen during life and in smears from the spleen at autopsy. These findings were soon confirmed by Rogers and many others.

In 1904, Laveran and Cathoire reported finding similar organisms in the spleen of a child in Tunis, who had been suffering from a febrile condition common in that place. The next year Pianese found the same parasite in the spleens of children in Italy affected with a form of splenic anemia. Nicolle in 1907 proposed the name "infantile kala-azar" for the disease as it occurred about the Mediterranean, and called its parasite the "*Leishmania infantum.*"

Cutaneous leishmaniasis under various local names, such as Oriental sore, Delhi boil, Aleppo boil, had been known in India since the eighteenth century. In 1903, Wright, of Boston, described bodies very similar to those found in kala-azar in a case of tropical ulcer occurring in a girl from Armenia. This organism has since been named *Leishmania tropica*, and is recognized as the causative agent of Oriental sore.

In 1909 Lindenberg, Carini and Paranhos described leishmania of the type of *Leishmania tropica* from ulcers in Brazil. This finding was subsequently confirmed by many workers in Brazil, Peru, Chile, and Guiana. Gaspar Vianna in 1911 described the parasite under the name "*Leishmania braziliensis.*" Strong and his collaborators in 1913 showed that uta, known in Peru since prehistoric times, is a form of leishmaniasis. The cutaneous form of leishmaniasis of South America differs from the oriental type in its greater tendency to involvement of the mucous membranes of the nose, mouth and pharynx.

Thus there have been described two forms of visceral leishmaniasis and two forms of tegumentary leishmaniasis. The visceral form in India and China affects principally adults, while that found in the countries about the Mediterranean affects chiefly infants. The parasites in the 2 cases are very similar.

Oriental sore and the American tegumentary leishmaniasis differ in the greater tendency for the latter to involve the mucous membranes. Their parasites are similar if not identical.

The discussion of the leishmaniases must therefore be taken up under four headings, *viz.*, (1) Indian kala-azar due to *Leishmania donovani;* (2) Infantile kala-azar, due to *Leishmania infantum;* (3) Oriental sore, due to *Leishmania tropica;* and (4) American tegumentary leishmaniasis, due to *Leishmania tropica*, var. *americana* or *Leishmania braziliensis.*

Causative Organism.—There is no morphological difference between the organisms producing the different forms of leishmaniasis. Attempts have been made to differentiate them by cultural methods and by the susceptibility of animals to inoculation, but these methods have also failed to show constant essential differences. Therefore it will suffice here to present only a brief summary of the work done along these lines.

The leishmania present a flagellate and non-flagellate stage. It is the non-flagellate form that is found in the tissues, while the flagellate stage develops in cultures and in the gut of infected insects and the latex of certain plants.

The non-flagellate form is found in the tissues of infected cases as a round, oval or pyriform body measuring 2 to 3.5 μ long and 1.5 to 2 μ wide. The granular protoplasm contains a rounded macronucleus and a more deeply staining rod-shaped micronucleus, or blepharoplast, which is placed in varying relations to the macronucleus. A rhizoplast has been described by some as arising from the micronucleus. The multiplication of this form of the leishmania occurs by division first of the macronucleus, then of the blepharoplast, and lastly of the cytoplasm. It is this form that is found in sections of tissues and in smears from the organs and blood.

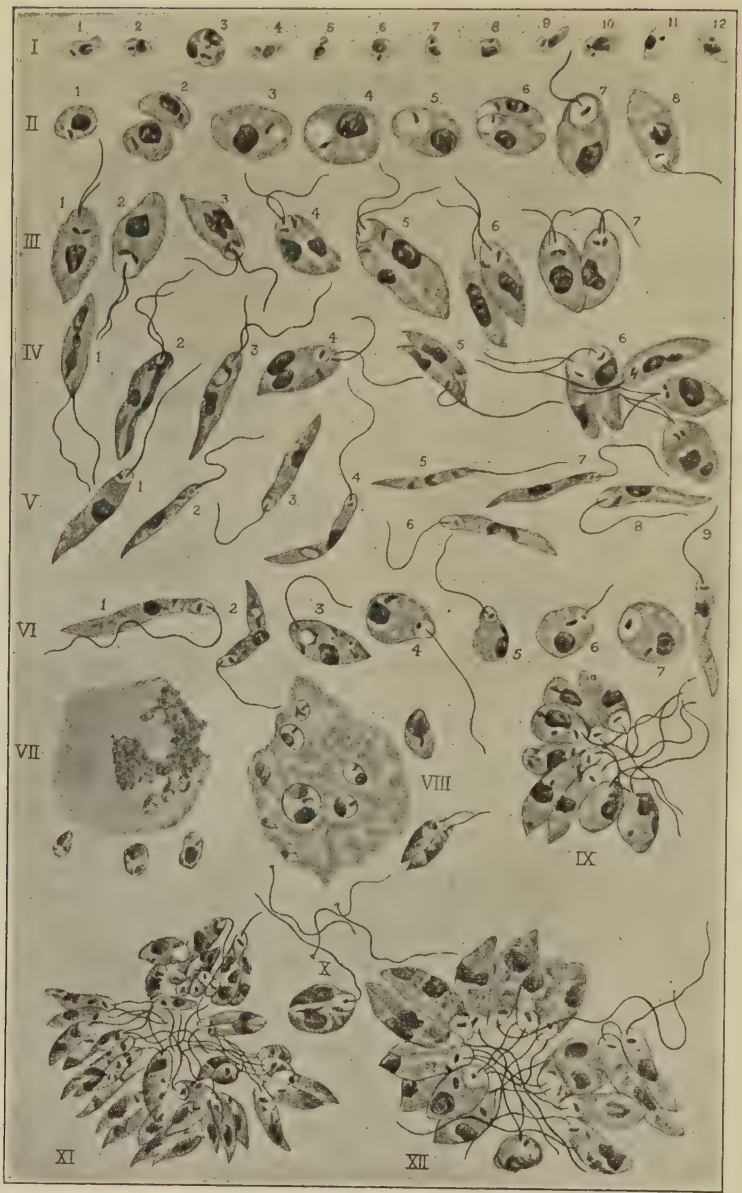
Rogers, in 1904, cultivated the organism at 22° C. and discovered the flagellate stage. Patton, in 1906, showed that the organism could develop into typical flagellates in the bedbug, *Cimex rotundatus.* The flagellate form has a dark blue, granular cytoplasm with a circular trophonucleus, which stains deeply in the centre, and a kinetonucleus lying across the long diameter, and situated near the trophonucleus, and possessing a long flagellum consisting of a number of filaments adhering closely together inserted into a pale area near the kinetonucleus. These parasites may divide into equal or unequal flagellate forms, and apparently may go on so dividing for a length of time (Castellani and Chalmers).

Nicolle and Comte, in 1908, found leishmania in dogs in Tunis, and the canine disease has since been found to be almost coextensive with the infantile type of kala-azar, but it is not abundant in the centres of greatest incidence of the adult type of the disease. Nicolle concluded that infantile and canine kala-azar are one and the same disease, and that it is transmitted by the dog flea *Pulex serraticeps.* Doubt has been thrown on this by subsequent work.

Donovan and Patton have recently successfully inoculated dogs with splenic material from kala-azar patients. Monkeys are susceptible to inoculation with *Leishmania donovani, Leishmania tropica,* and *Leishmania infantum.* Dogs can be infected with *Leishmania tropica,* but in them we have only cutaneous lesions produced. White mice may be infected with kala-azar and Oriental sore, there being produced in each case a general infection with the presence of parasites in the liver and spleen.

While the above is a statement as to the susceptibility of animals to

FIG. 56



I, Undeveloped Leishman-Donovan bodies from spleen-puncture film; II, early stages of development, from two days' culture in acidified citrated blood; 1 and 2, body and macronucleus enlarged; 3 and 4, first appearance of eosin body; 5 and 6, elongation and subdivision; 7 and 8, first appearance of flagellum; III, stages of division of the early flagellated forms; IV, double, long, swimming forms; V, fully developed, long, free, active single cells; VI, degenerate forms; VII, undeveloped forms in a white corpuscle; VIII, early stages of development in a degenerating white corpuscle; IX, stage in the formation of rosette; X, separated flagella with micronuclei attached; XI, rosette breaking up into free forms; XII, small complete rosette. (*Magnification of all the figures 1500 diameters.*) (Rogers.)

leishmania from various sources, it is seen that the possibility of animal inoculation has not greatly enhanced our knowledge as to specific differences in the parasites concerned. Much work on the transmission of the disease has been done since Patton, in 1906, showed that the parasite of kala-azar could develop into typical flagellates in the bedbug. The names of Mackie, Wenyon, Cornwall, Menon, Da Silva, Basile, San Giorgi, Sergent, Gabbi, Marshall, Massaglia, Franchini, Laveran, Cerqueira, Walker and Aragão may be mentioned among those who have done work bearing on the transmission of the disease and the life of the parasite in insects. Bedbugs, fleas, flies and mosquitoes have been among the insects studied. However, it may be said that conclusive evidence from this work has not yet been presented to show the natural method of transmission of the disease, or specific differences between the species of leishmania. Stitt states that epidemiological evidence supports the bedbug transmission for Indian kala-azar.

Darling maintains that the organism is identical with *Herpetomonas*, a group of flagellates which parasitize insects and are also found in the latex of certain plants. Fantham and Porter also say that "it may be expected that the various leishmaniases, occurring in different parts of the world, will prove to be insect-borne herpetomoniases."

A. KALA-AZAR.

Definition.—Kala-azar is a chronic infectious disease occurring in endemic and epidemic forms, characterized by fever, anemia, emaciation, enlargement of the spleen and liver, and caused by *Leishmania donovani* (R. Ross 1903).

1. **Indian Kala-azar.**—**Synonyms.**—Tropical splenomegaly, Tropical splenic anemia, Sirkari disease, Sahib's disease, Dum-Dum fever, Visceral Leishmaniasis.

Geography.—The disease is found in India and Ceylon, Burma, Indo-China, China, Sudan and Arabia. In India the adult type is found especially prevalent in the eastern part, Assam, Madras and Bengal, whereas the infantile type is more common in the western part. It also occurs in Italy, Greece, Cyprus, Turkey, Syria, Mesopotamia, Portugal, Spain and Northern Africa, but in these latter countries it is the infantile type that predominates. The highest incidence of the adult type has been in Assam. The studies of Archibald seem to show some peculiarities in the type encountered in the Sudan.

Etiology and Transmission.—These have been discussed in the introduction to this article. There are certain predisposing factors. The disease occurs only in warm countries, with the exception of occasional imported cases outside of the tropics. It attacks both sexes and all ages. It has been noted that in the Mediterranean countries infants especially are affected, while in India and China adult cases predominate. In Assam, Rogers found nearly 70 per cent. of the cases under twenty years of age. In Calcutta, among natives, he found 4 per cent. under ten years, 40 per cent. between ten and twenty years, 32 per cent. between twenty and thirty years, 16 per cent. between thirty and forty years, and only

4 per cent. over forty years of age. There is no known racial immunity, but the disease shows a predilection for natives. The method of transmission is unknown. (See introduction.) Rogers holds that the great majority of the cases become infected during the cold season. There is a remarkable tendency to the familial incidence of the disease.

Pathology. – At autopsy the chief changes found in the body consist in great emaciation, generalized œdema, enlargement of the spleen and liver, red bone-marrow, and changes in the other viscera dependent upon the protracted severe anemia. Intestinal and cutaneous ulcerations are frequent, and hemorrhages often occur. Complications with malaria, intestinal parasites and pyogenic infections are frequent.

The characteristic changes are produced by the presence of *Leishmania donovani* which enter the endothelial cells especially of the spleen, liver, and bone-marrow and there multiply.

Meleney has studied kala-azar in China and reports a study of the disease in 19 hamsters, 2 monkeys, and 2 human cases. He concludes that the specific reaction to the infection consists of endothelial proliferation and the formation of solid masses of clasmatocyte tissue. The liver, spleen lymph nodes and bone-marrow are the chief sites of formation of this tissue. Parasitized clasmatocytes appear in the connective tissue of practically all of the organs and tissues.

As regards the distribution of the parasites Laveran found that after the blood-forming organs, the lymph nodes and lymphatic tissue in other organs next became involved, then the organs whose loose areolar tissue normally contains many small bloodvessels and wandering cells. Thus the intestines, testes, lungs, adrenals, pancreas, skin, kidneys and meninges are likely to become involved in about the order named.

Meleney draws attention to the similarity of the character of the reaction to leishmania with that to typhoid fever and Darling's histoplasmosis. The author has described the lesion in American trypanosomiasis in animals and humans, and the character of the reaction bears a very remarkable similarity to that described by Meleney in kala-azar. The most frequent site of the parasite in the chronic human cases, however, differs in the two diseases.

It is very obvious that the chief reaction and chief parasitization is on the part of the reticulo-endothelial system of Aschoff.

The *spleen* is much enlarged, at times enormously so. According to Laveran the capsule of the spleen is generally smooth, distended and without adhesions to the neighboring parts. The consistence of the parenchyma is variable; in the acute cases the pulp is soft and protrudes when the capsule is incised. Spontaneous rupture sometimes occurs. In the cases with slow progress the spleen increases in consistence, the capsule thickens and ruptures are less frequent. The spleen has a solid appearance and preserves its form after removal from the body. Its substance is deep red, granular and hemogeneous. The trabeculæ are clearly seen on the dark red pulp. It is firm to the touch but very friable, very different from the fibrous spleen. The reddish-violet color of the parenchyma is clearly distinguished from the slate-colored tint occurring in malaria. On section of the spleen, the Malpighian corpuscles some-

times appear hypertrophied, and sometimes are scarcely visible. The connective tissue is not prominent in the acute cases but becomes prominent in the chronic ones.

Microscopically, Christopher has emphasized the important role of the endothelial cells lining the capillaries and venous sinuses. These become filled with the parasites and much enlarged. Mononuclear and polynuclear leukocytes may also be found parasitized. With the freeing of the parasites from the ruptured endothelial cells their phagocytosis occurs. This process is similar to that occurring in the spleen infected with *Trypanosoma cruzi*. Smears made from the spleen form one of the most ready methods of diagnosis. In the later stages there are described atrophy of the lymph follicles, thickening of the reticulum, hemorrhages and general fibrosis.

The *liver* is usually enlarged but proportionately less so than the spleen. The surface is smooth and red, mottled with paler areas. The consistence is firm. The appearance of the cut surface resembles that of a nutmeg liver but is lighter. Paler areas may be seen corresponding to collections of parasitized endothelial cells. Rogers has described an intralobular cirrhosis in cases of long standing, thus accounting for the ascites which occurs in the terminal stage of many of the chronic cases. Microscopically the structure of the lobules may be destroyed and the striking feature is the presence of the parasites in the endothelial cells of the sinusoids. These are the Kupffer cells, so well known from their phagocytic properties. Infarction of the liver sometimes occurs.

The *intestine*, especially the large intestine, is frequently the seat of ulcers which vary in size from small erosions up to larger ulcers which may perforate. Congestion of the mucosa is frequent. There appears to be nothing characteristic about the intestinal ulceration. The parasites have been found in scrapings from, and sections of, these ulcers.

The *lymph nodes* are often enlarged, but not greatly so, The mesenteric nodes seem to be those chiefly involved. The microscopic changes are analogous to those in the spleen. The parasites are said not to be as numerous as in the spleen.

The *marrow* of the long bones is red, soft, and diffluent. Parasitization of endothelial cells and macrophages is present, and there is the usual reaction of the bone-marrow to a severe anemia.

The parasites may be found in any of the other viscera, but their number is not usually great. There occurs in the organs other than those above mentioned no change which is known to be characteristic of this disease other than the appearance of parasitized clasmatocytes which may be present in the connective tissue of practically all organs and tissues. Attention has been especially drawn to massive accumulation of paratized cells in the stroma of the intestinal mucosa.

Symptoms.—The period of incubation varies from about three weeks to several months after exposure to infection. Manson mentions 1 case in which it apparently lasted less than ten days.

The onset is usually with fever which is usually accompanied by a rigor. Nausea is uncommon. The initial fever may be very severe, and is remittent or intermittent in character. Rogers says that there is a

marked tendency for two, or sometimes three, rises in temperature during the twenty-four hours, thus permitting early differentiation from typhoid fever. The period of initial fever lasts from two to six weeks or longer, and is followed by a period of apyrexia and general improvement, to be followed by other periods of pyrexia. Such periods alternate for months until at last a low form of fever becomes persistent. During the period of initial pyrexia the spleen, and to a less extent the liver, enlarges, and may show fluctuation in size with the alterations in the temperature. These organs may become tender. Other symptoms, except headache, in about one-fourth of the cases, are usually absent during the early stages. The spleen usually reaches below the costal margin in less than a month, and the enlargement of the liver occurs more slowly. Rogers says that the spleen is usually hard, and in very chronic cases its firm edge may project so as to be evident to sight through the abdominal wall. Emaciation, anemia, œdema, especially of the legs, and often ascites ensue, giving a characteristic picture of the disease. Pigmentation of the skin of an earthy hue is frequent. The pulse is usually over 100, but shows nothing of diagnostic importance. Diarrhœa and later dysentery are frequent symptoms in the later stages.

The anemia becomes clinically prominent only in the later stages of the disease, the red cells seldom falling below 2,500,000 in less than six months. Severe anemia is usually unfavorable for the prognosis. The percentage of the hemoglobin falls in much the same proportion as the number of red cells (Rogers). Leukopenia is the rule, and more than 3000 leukocytes per cubic millimeter are seldom found. Polynuclears and eosinophiles are reduced and there is a relative increase in the proportion of large mononuclears and lymphocytes. The proportion of leukocytes to red cells is much reduced. Instead of the usual proportion of white to red cells, *viz.*, 1 to 750, Rogers found nearly 90 per cent. in which the ratio was less than 1 to 1500. This blood picture is considered by Rogers as a valuable aid in diagnosis. The coagulability of the blood is decreased, and this should be remembered when contemplating diagnostic splenic puncture.

Complications.—Complications usually terminate the disease. Cancrum oris and other septic conditions are the most frequent complications, pneumonia is next most frequent and fatal, while bacillary dysentery, tuberculosis and hemorrhages occur frequently. The disease in India usually lasts from one to two years. In the Sudan some cases have a much more acute course.

Diagnosis.—The absolute diagnosis rests on the isolation of *Leishmania donovani*. Shortt has recently given a list of the methods used in the diagnosis of kala-azar in their order of relative reliability as follows: (1) Culture of the spleen or liver puncture fluid on the N. N. N. medium; (2) culture of the peripheral blood by Row's method or on N. N. N.; (3) examination of the spleen or liver puncture films, no cultures taken; (4) the aldehyde reaction, and (5) examination of peripheral blood films, no cultures taken.

Puncture of the liver is generally regarded as a safer procedure than puncture of the spleen. Coagulability of the blood is reduced in this dis-

case, and should render one cautious on account of the liability to hemorrhage. By the aid of a small dry needle and syringe, a drop or two of the juice of the organ may be withdrawn for examination. Rest in bed and the application of an aseptic pad and a firm bandage for some time after puncture is performed is advised. Rogers advises the administration of 30 gm. of calcium chloride in 2 ounces of water immediately after the puncture to promote coagulability of the blood.

The organism cannot always be isolated from the peripheral blood, hence the necessity in doubtful cases for organ puncture. Cochrane in China advises gland puncture or enucleation of a gland for diagnostic purposes.

Kligler and Noguchi and Lindenberg have reported the successful cultivation of *Leishmania braziliensis* on Noguchi's medium for the cultivation of organisms of the leptospira group of spirochetes, and it is possible that this medium may serve for *Leishmania donovani*.

The aldehyde, or formol-gel, test consists in adding 1 or 2 drops of formalin to the serum from 2 cc. of blood. If the reaction is positive within one-half hour the serum will solidify into a white opalescent jelly something like boiled white of egg. The time-period of one-half hour must be adhered to in considering the reaction positive. This reaction may be negative in early cases of kala-azar or in very young patients, but when the case is well advanced a marked positive reaction is said to be present in 95 per cent. of the cases. Aside from these laboratory tests the clinical features of the disease outlined above may in themselves be sufficient for diagnosis.

Differential Diagnosis.—The diseases most likely to be confused with adult kala-azar are malaria, typhoid fever, hookworm disease, Malta fever, leukemia, and other forms of splenomegaly. There are specific tests for each of these diseases which are commonly known.

Prognosis.—Until the advent of the use of tartar emetic the mortality was 98 per cent. This figure has been much reduced, as will be referred to in the next paragraph.

Treatment.—Former methods of treatment have given uniformly discouraging results. Tartar emetic was used by Vianna in Brazil in the treatment of tegumentary leishmaniasis, and its use in kala-azar has proven very successful. Di Cristina and Caronia, Rogers and Hume, Knowles and others have reported good results. Rogers uses the less toxic sodium salt of antimony.

Tartar emetic (tartrate of antimony and potassium) made up in 1 per cent. solution in normal saline solution and autoclaved at 110° C. for ten minutes only is used. Knowles begins in an adult with an intravenous injection of from 3 to 4 cc. on alternate days. This dosage is gradually increased until from 10 to 12 cc. are given. In a course of treatment a total of 200 cc. are administered over a period of seventy to ninety days. Castellani and Chalmers give the following instructions: "Give 2 to 10 cc. of a sterile 1 per cent. solution in warm normal saline solution daily intravenously for five to ten days, and then every other day, and finally twice a week. This is the best method of treatment."

INTRAVENOUS DOSAGE FOR CHILDREN OF 1 PER CENT. TARTAR EMETIC SOLUTION.

Age.	Dose.	Number.
Under one year	¼ to 1 cc.	One daily for seven days.
One to five years	1 to 3 cc.	One daily for seven days.
Five to ten years	1 to 5 cc.	One daily for seven days.
Ten to sixteen years	1½ to 8 cc.	One daily for seven days.

"*Important.* –The sterilization of the tartar emetic solution must be made in flowing steam on two or three consecutive days and must not be performed in an autoclave, in which the drug is liable to decomposition and may then cause serious symptoms."

When the remedy is being introduced into the vein, great care should be taken to avoid leakage into the tissues as the drug is very irritating. The use of tartar emetic is not without danger, as a few fatalities have followed its use. However, these are so few compared to the very great number of administrations of the drug that it should not prevent its use when indicated. Aside from the specific treatment the patient should be kept in bed and well nourished. Symptomatic treatment may supplement the specific treatment.

During the last two years excellent results have been reported from India from the use of Urea Stibamine in the treatment of kala-azar.

Europeans should be sent outside the endemic region for completion of treatment.

As the method of infection is unknown segregation of the sick and protection against blood-sucking arthropods should be practised. Removal of the healthy from the infected area and care of the drinking water should also be effected.

2. **Infantile Kala-azar.**—Infantile kala-azar is now generally conceded to be the same disease as the adult type encountered in India. On account of its preponderating incidence in children in Tunis and Italy, Nicolle, in 1907, gave it the name of Infantile Kala-azar and called its causative organism *Leishmania infantum*. At the same time the organism was found in dogs in Tunis, and it was considered that the disease was transmitted by the dog flea. A much higher percentage of dogs was found infected with the organism in Tunis, Italy, Sicily and other Mediterranean countries than in India. Certain cultural differences between *Leishmania donovani* and *Leishmania infantum* were described, and the susceptibility of animals to inoculation with the two organisms was considered different. Subsequent work has almost, if not completely, disproved these differences as forming essential differentiating features between the disease as found in India and the Mediterranean countries and between their organisms.

In work done on the possibility of transmission of the disease, the spontaneous occurrence of herpetomonads in the gut of the insects under investigation should always be considered. Immunity experiments by Laveran in a monkey showed no difference between *Leishmania infantum* and *Leishmania donovani*.

The symptoms and course of infantile kala-azar are similar in all respects to those of the adult type produced by *Leishmania donovani*.

B. TEGUMENTARY LEISHMANIASIS

1. **Oriental Sore.**—**Synonyms.**—Delhi boil, Aleppo boil, Biskra boil, Bouton d'Orient, Ulcera de Bauru, Endemic boil disease, Pian-Bois, Cutaneous leishmaniasis, etc.

Definition.—An ulcerative lesion of the skin caused by *Leishmania tropica* (Wright). For purpose of description this condition will be considered separately from the mucocutaneous leishmaniasis of South America.

History.—This disease was described as Aleppo boil by several authors during the eighteenth century, by whom it was believed to be caused by the drinking water. Hirsch says that Virchow was the first to suggest a parasitic cause. Numerous organisms were described as causative agents prior to Wright's description of the leishmania which is now recognized as the true cause. In 1885, Cunningham described parasites which were frequently endocellular, and readily stained with gentian violet, in cases of Oriental sore, which he regarded as probably mycetozoa. It is considered possible that these organisms seen by Cunningham were really the leishmania. Borowski, in 1898, described bodies obtained from 20 cases of the "Sarten Boil." These answer well to the description of *Leishmania tropica*. It was in 1903 that Wright, of Boston, described bodies very similar to *Leishmania donovani* in a case of an ulcer occurring in a girl from Armenia. The finding of this organism has been confirmed by many workers and it is generally accepted as the etiological agent of the disease. In 1908, C. Nicolle and A. Sicre succeeded in cultivating the organism. In 1908 and 1910, C. Nicolle and his collaborators successfully inoculated Oriental sore into monkeys and dogs; in 1913 and 1914, Gonder, Row and Laveran infected mice and other small rodents with *Leishmania tropica* in the flagellate and non-flagellate stages.

Geographic Distribution.—The disease has its highest incidence in tropical and subtropical countries, and is most frequently found in the following places: Syria, Asia Minor, Caucasus, Transcaucasia, Persia, Mesopotamia, Turkestan, western part of India, Algeria, Tunis, Sudan, Egypt, various interior parts of Africa, Italy, Greece, Spain, Crete, Sicily and South America. Imported cases are seen elsewhere, and it is probable that familiarity with the disease will show it in places where it is not now recognized.

Predisposing Causes.—The influence of season is very marked. The disease is most prevalent after the hot summer months and during the rainy season of September, October and November. In India the boils appear principally during the cool season. Race, social status and physical condition exert no influence on the occurrence of the disease. As regards age, the sore may attack persons of all ages, but it is during the first three years of life that most cases occur. In Aleppo it is rare for a child to reach its seventh year without being infected. It has been noted that while the disease is frequent in some towns, it may be quite unknown in other places a few miles distant, or that there exist certain endemic foci of the disease.

Immunity.—Earlier opinions differed as to the immunity conferred by an attack of Oriental sore. It is said that the Jews of Bagdad were in the

habit of inoculating children on the legs with the virus from a sore so that they might avoid naturally contracted sores on the face with their associated disfiguring scars. It is now generally held that one attack does confer immunity, and experimental work with dogs and monkeys confirms this.

Transmission.—Oriental sore is inoculable in man and animals, notably dogs, monkeys and mice. It is also auto-inoculable and patients transfer the virus from one part of the body to another on their nails in scratching. The lesion frequently develops on preëxisting sores, and the virus may be transmitted on soiled linen. The role of insects in the transmission of the disease is not clear. The first lesions usually occur on parts of the body unprotected by clothing, and this speaks in favor of insect transmission. Bedbugs, mosquitoes, the phlebotomus, and the ordinary house fly have been incriminated, but actual transmission in this way as an important epidemiological factor has not been proved.

The question of a reservoir of the virus in animals has been discussed. Spontaneous infection of dogs in some places is known to occur, but infected patients seem to constitute the important, if not the only, reservoir of the virus.

Gonder has suggested that Oriental sore, like kala-azar, is really a general infection overlooked in its earlier stages, and that it is in the later stages that peripheral lesions on the skin are developed. Row obtained a general infection in a mouse by the injection of culture of *Leishmania tropica* from Oriental sore.

The Organism.—*Leishmania tropica* occurs in the flagellate and the non-flagellate stage. In the latter stage there is no morphological difference between the *Leishmania tropica and Leishmania donovani.* In the flagellate stage that occurs in cultures some workers have claimed morphological differences between the two types, but these differences are not considered sufficiently important to characterize two different species.

The geographic distribution of kala-azar and Oriental sore seem to Laveran to indicate that they are different diseases. And Laveran further states that the two diseases never complicate one another. There is some evidence that there is no cross immunity between the two diseases, but this question still remains open. The description of the organism may be seen in the section on Kala-azar.

Pathology.—The histological changes are not sufficiently characteristic to permit of an absolute etiological diagnosis from sections of the tissue without the finding of the parasite. There occurs an atrophy and disappearance of the epidermis and a dense infiltration of the corium extending into the papillæ and about the sebaceous glands and hair follicles. At times there is very great, and irregular, proliferation of the epithelial pegs downward. The infiltration is composed of lymphocytes, plasma cells and large mononuclear cells. It is in these latter cells that the parasites are found most abundantly and characteristically, the number of parasites in the cell varying up to twenty or more. Giant cell formation sometimes occurs. When many of the parasites are crowded together in one cell they may be so compressed or deformed that details of their individual structure may be difficult to see, but usually some of them will show the

characteristic macronucleus and blepharoplast. While the Giemsa stain is usually given the preference for staining the sections, the author has obtained very clear pictures with hemotoxylin and eosin.

Incubation Period.—Experimental inoculation of man has resulted in the following periods of incubation: seventy days (Marzinowsky), seven months (C. Nicolle and Manceaux), seven weeks and six and a half months (Wenyon), sixteen days (Patton).

Natural infections occurring in one who has only passed through an endemic focus or one who has developed the disease after leaving an infected place have given incubation periods of fifteen days and five months.

Laveran states that there is no authentic example of an incubation period of more than seven months.

Symptoms.—The Oriental sore develops almost always on a part of the body that is ordinarily uncovered, as the face, neck, ear, forearms and legs. Other parts of the body may become involved by auto-inoculation.

In the initial stage there develops a small nodule in the skin which is firm and painless. Itching is a prominent symptom. This becomes elevated above the surface and surrounded by a red zone. It is the rule for several of these nodules or tubercles to develop in the immediate vicinity of one another. Slight fever and some digestive troubles are sometimes noted during this initial period. Some of the lesions progress no further than this nodular stage but usually there ensues ulceration, the extent and appearance of the ulcers varying according as to whether there were one or more primary nodules. A dry crust or scab forms over the ulcer and this becomes thick and brown. On removal of the crust a round or oval ulcer is exposed, the base of which is usually covered with a fetid pus. There is frequently a central ulcer surrounded by a number of small papules at the margin. These ulcers may attain a diameter of 8 or 10 cm. As healing occurs the ulcer becomes more and more shallow, and cicatrices form from the periphery with considerable deformity and pigmentation. The duration of the lesion is from several months to a year and a half. The chief complication is a lymphangitis with erysipelas.

Diagnosis.—The diagnosis is made by finding the *Leishmania tropica* in smears or sections of tissue. As a rule they are more readily found in smears than in sections. The number of organisms, and the facility with which they are found varies in different cases and according to the stage of the ulceration. Scrapings from near the margins seem to show the organisms in greatest numbers. Some modification of the Romanowsky stain is best for their identification.

No one description of the appearance of the sores can adequately depict the diverse forms that they may assume. Many cutaneous lesions may be imitated, hence the necessity for isolation of the parasite in every case. Treatment may lead to a rapid disappearance of the parasites. Cultivation of the parasite may be accomplished directly from the lesions on N. N. N. medium, or on the Noguchi medium for the cultivation of organisms of the leptospira group of spirochetes.

Treatment.—The treatment consists in the administration of tartar emetic intravenously. This is prepared in 1 per cent. solution in normal

saline solution. If autoclaved it should be at 110° C. for ten minutes only. Sterilization in flowing steam on successive days or filtration through a Berkefeld filter is preferable. Castellani recommends daily doses of 5 to 10 cc. of the solution for five to ten days, then every other day or twice a week until 15 to 30 injections have been given. In chronic cases Chagas advises that the injections be given in series with intervals of rest to avoid the phenomena of intoxication and intolerance. In Brazil it is customary to supplement the intravenous medication by topical application of the same 1 per cent. solution to the sores. As a rule a tolerance for the drug is easily established, but its administration should always be undertaken with a knowledge of the symptoms of intoxication by the drug and of the fact that a few cases of sudden death have been ascribed to its use.

2. **Tegumentary Leishmaniasis.—South American Mucocutaneous Form.**—The recognition of this disease in Brazil was accomplished by a dermatologist, Adolpho Lindenberg, who found a protozoön that he considered identical with *Leishmania tropica* in ulcers of an etiology that was until then unknown. Moreira, in 1896, had reported the occurrence of this condition in Brazil, but the pathogenic agent was not known at that time. In Brazil the condition is known by the natives under various names, such as Botão de Bauru, Feridas bravas and Espunja. The disease has also been identified in other South American countries, the Argentine, Paraguay, Uruguay, Chile, Peru, Colombia, Ecuador, the Guianas and Venezuela, and in Central America and Mexico. In Chile the disease is known as Espundia, and in Peru as Uta, and these lesions have been traced to prehistoric times by paleopathologists. It seems certain that the conditions known under these various names in different parts of South America are all the same disease. The list of authors who have contributed to our knowledge of the disease in South America is a long one and contains such names as those of Moreira, Lindenberg, Chagas, Carini, Torres, Aragão, Rabello, Darling, Escomel, Splendore, Tamayo, Laveran, Nattan-Larrier, Strong, Breda, Klotz and Montenegro.

A few cases in which Oriental sores have attacked the mucous membranes of the lips, mouth and nose have been reported from the eastern hemisphere, but these have not had the clinical course ordinarily seen in American leishmaniasis. A single case of an individual who had lived in India has been described by Castellani and Chalmers under the name of Indian oropharyngeal leishmaniasis, but that the leishmania found in the case was *Leishmania tropica* has not been proven.

The Organism.—No essential morphological difference between *Leishmania tropica* and the causative agent of South American leishmaniasis is recognizable, nor are they with certainty to be differentiated by any other means than by the course of the disease they produce. It is on this basis that Laveran and Nattan-Larrier proposed the name *Leishmania tropica* var. *americana*. Vianna had previously proposed the name *Leishmania braziliensis* on account of the finding of a rhizoplast, but this was also found to be present in *Leishmania tropica*.

Transmission.—The disease may be transmitted from one individual to another by direct contact. This was known on epidemiological grounds, and has been well proven recently by Montenegro who showed that (1)

healthy individuals can be successfully inoculated by the material obtained from a sick one; that (2) inoculations of leishmania culture in an already infected person were negative, and that (3) the incubation period was about three weeks.

The possibility of its being transmitted by biting insects has always held a prominent place in the minds of South American workers, and tabanids, mosquitoes, phlebotomus and ticks have been especially inculpated. Epidemiological facts may be brought forward to favor these ideas, but definite proof of the role of these insects in the transmission of the disease is still lacking.

Symptoms.—As in the Oriental sore of the eastern hemisphere, the initial lesion in this American type appears on the uncovered parts of the body as a localized area of erythema and induration of the skin which goes on to ulceration. The ulcerating area widens until it attains a diameter of 2 to 6 cm. or more. The borders are not undermined, the margins but slightly raised, and the outline is round or irregular. A crust is formed beneath which there is abundant granulation tissue in the early stages. Later the floor of the ulcer becomes smooth, red, and clean, and the ulcer may remain in this state for years. Klotz has drawn attention to the fact that nodules may be felt along the lymphatics draining the ulcer, and that these nodules may ulcerate. Instead of the formation of ulcers one sometimes sees the development of large cauliflower masses projecting above the skin. The duration of the ulcers varies up to many years.

At periods varying from some months to many years after the appearance of the ulcer of the skin, there appear lesions of the mucous membrane of the nose, pharynx and larynx. At the time of appearance of these lesions of the mucosa the initial ulcer may still be present or may have already cicatrized. In the state of São Paulo, in Brazil, it is said that 15 to 20 per cent. of cases in which the skin lesions are more than two years old develop the involvement of the mucous membranes. These secondary lesions of the mucosa appear to be true metastatic infections.

The following description of the peculiar involvement of the mucous membranes, which is characteristic of the disease, is taken from the work of Klotz and H. Lindenberg. "The nose lesion begins beneath the mucous membrane covering the cartilaginous septum. It begins within the nose and does not commence in the skin covering the nose, and seldom at the entrance of the nares. The first evidence is recognized in a slight œdematous swelling and reddening of the mucosa. The swelling slowly increases and becomes harder. The passage is partly occluded. Ulcers then appear on the surface of the septum and a purulent discharge incrusts the involved part. The ulcer then spreads in its periphery, extending backward to the palate and pharyngeal wall, as well as downward to the nasal opening. The progressive ulceration is accompanied by considerable destruction of the deep tissues so that the cartilaginous septum becomes perforated, the alæ of the nose eroded and the palate scarred and distorted. Much deformity may thus be induced.

"The progress of the ulcers is slow, usually a matter of some years. The extension into the pharynx may reach as far as the larynx, destroy-

ing portions of the epiglottis as well as the vocal cords. The mucosa of the mouth, tongue and fauces may also become involved. During the progress of the nasal and pharyngeal ulceration there may be little influence upon the general health of the patient. Fatal cases result more commonly from intercurrent diseases, particularly from bronchopneumonia."

Pathology.—The histopathology of the cutaneous lesions differs in no essential respect from that already described for Oriental sore. The nature and progress of the tissue reaction found in the nasal mucosa has recently been accurately described by Klotz and H. Lindenberg, as follows: "The lesion is one of a peculiar granuloma, having individual and characteristic tissue reactions, and passing through successive stages. The parasite of the disease, which can be demonstrated in the various phases of the development of the granuloma, has *per se*, only moderate destructive action upon the tissues. The destruction of the soft tissues and cartilage is to a great extent brought about by the progressive local endarteritis causing nutritional atrophy and necrosis. The tissue reaction due to the parasite never causes a purulent inflammation, such as occurs with blastomyces and actinomyces, and a fair amount of scar tissue is produced at the border of the involved area.

"The manner of development of the lesion of the nose suggests a metastatic distribution from the primary ulcer on the arms or legs. On the other hand, the centrifugal spread from the earliest point of infection, and the microscopic character of the local process suggests a lymphatic dissemination of the immediate neighborhood.

"The granuloma beginning as a perivascular lymphocytic infiltration of the submucosa, passes through stages in which the plasma cells and endothelial cells gradually gain dominance, and ends with the development of nodules largely composed of endothelial cells. These nodules may show central necrosis, or may undergo fibrosis. In the late stages, the accompanying endarteritis of the neighboring vessels leads to extensive ulceration and necrosis. The leishmania is almost constantly to be found intracellular, within endothelial cells."

Diagnosis.—The diseases which this condition may simulate in some respects are especially blastomycosis, syphilis, tuberculosis, gangosa, leprosy, framboesia. However, its clinical course is different from that of any of these diseases, and the absolute diagnosis rests on the finding of the leishmania by some of the methods outlined above.

Treatment.—This differs in no respect from that described for Oriental sore.

PART III

SPIROCHETAL INFECTIONS

CHAPTER XV

SYPHILIS

By the late Sir WILLIAM OSLER, M.D.

AND

JOHN W. CHURCHMAN, M.D.

REVISED BY

LEWIS A. CONNER, M.D.

Synonyms.—Lues Venera, Bad Disorder, Pox, Morbus Gallicus; French, Verole; German, Lustseuche, Krankheit der Franzosen; Italian, Sifilide; Spanish, Sifilis; Swedish, Radezyge.

Definition.—Syphilis is an infectious disease, acquired by contagion or transmitted from the mother to the fetus, which runs a chronic course and exhibits local and general constitutional manifestations. Its signs and symptoms are protean, but they are often exhibited in a determinate order, on the basis of which several distinct clinical stages are recognized. The lesion produced is an infectious granuloma, similar to that seen in tuberculosis and leprosy.

History.—That venereal disease existed among, and was known to, the ancients is shown in the medical and lay writings of those times and in various passages in the Old Testament; but the weight of evidence at present seems to support the contention that syphilis is of American origin and was introduced into the continent of Europe by the Spanish sailors under Columbus upon their return from their sojourn in Haiti during his first voyage. Certain it is that the first known pandemic of that disease started in Italy during the invasion of that country by the army of Charles VIII (1494–1495) and that the spread of the pandemic through Europe coincided with the retreat of that ill-fated army and the return of its mercenaries to their widely scattered homes. There is evidence that the port of Barcelona was infected by the sailors of Columbus' fleet and that the army of Charles contained many Spaniards. The extremely virulent character of the disease during this epidemic seems to lend support to the view that the seed had been sown on virgin soil.

The assertion that undoubted evidences of syphilis are to be found in bones of great antiquity has not gained general acceptance. The view has been held in some quarters that syphilis as seen in Europe is a modified form of yaws transported from the west coast of Africa.

For more than three centuries after the appearance of this epidemic confusion existed as to the relation to each other of syphilis, chancroid and gonorrhœa. It was long held that in each of these the virus was identical and this view seemed to be confirmed by the self-inoculations made by John Hunter. The experiments of Bell and especially of Ricord (1838) finally established the dual nature of gonorrhœa and lues. In the treatment of syphilis mercury and guaiacum came into general use in the sixteenth century and potassium iodide in the early part of the nineteenth.

Within the past twenty years our knowledge concerning the diagnosis and the treatment of syphilis has received additions of enormous importance in the discovery by Schaudinn and Hoffmann of the cause of the disease, the practical application by Wassermann of the complement-fixation test to its diagnosis and the introduction by Ehrlich of salvarsan and allied arsenical compounds in its treatment.

Etiology.—Incidence.—Although for obvious reasons accurate figures concerning the incidence of syphilis are difficult to obtain, there can be no doubt that it is one of the commonest of the serious chronic diseases. On clinical grounds alone Neisser reckoned that not less than 12 per cent. of the adult population of Berlin was syphilitic, and Fournier, for the adult inhabitants of Paris, placed the percentage of those who had had the disease at fifteen. Figures based upon the results of many thousands of routine Wassermann tests in hospitals of this country show that a positive reaction is found in from 15 to 30 per cent. of all patients. The percentages of positive reactions in hospitals for children seem rather higher than in those for adults. Greeley states that among 1117 Wassermann tests of supposedly healthy applicants for license to peddle in New York City a positive reaction was obtained in 8.4 per cent. Vedder,[1] in his investigation into the prevalence of syphilis in the United States Army, gives the percentage of undoubted and probable syphilitics among recruits as 16.77, among white enlisted men as 16.08, among colored enlisted men as 36, and among soldiers of the Porto Rico Regiment as 55.93. He estimates that about 20 per cent. of the young male population of the class from which the Army is recruited is infected with syphilis. Among 4880 autopsies at Bellevue Hospital during a period of ten years Symmers[2] found anatomical evidences of syphilis in 314 cases (6.5 per cent.). On the other hand, Warthin[3] at Ann Arbor detected signs of syphilis in 40 per cent. of 750 autopsies performed by him. This marked discrepancy is obviously due, in large part at least, to the difference in the criteria used to establish the diagnosis. If Warthin's views should prove to be correct, then syphilis must be vastly more common throughout this country than has hitherto been supposed.

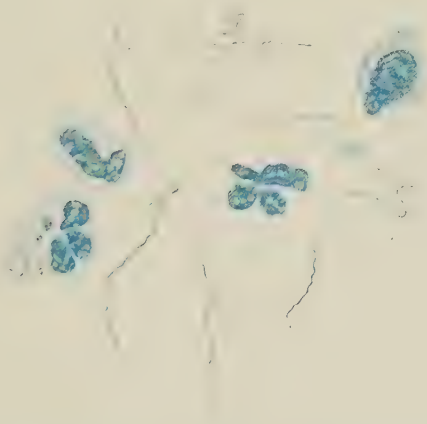
[1] *U. S. War Dept. Office of Surg. Gen.*, Bulletin No. 8, 1915.
[2] *Jour. Am. Med. Assn.*, 1916, **66**, 1457.
[3] *Am. Jour. of Syphilis*, 1918, **2**, 425.

PLATE IV

FIG. 1

Spirochæta Pallida. Smear from Hard Chancre.
Giemsa's stain. × 1000.

FIG. 2



Spirochæta Refringens. Smear from Chancroid. × 1000.

The Causative Agent.—The story of the search for the cause of syphilis is a tale to make the judicious grieve. "One hundred and twenty-five causes of syphilis," said Lassar in 1905, "have been established during the last twenty-five years." The idea of a living contagium as the cause of syphilis is of course an old one. The story of its "discovery" began in the seventeenth century with the finding, by Kircher (1658) and Abercromby, of a contagium animatum (vermiculi); and it continued almost without interruption until the last chapter was written by Schaudinn and Hoffmann. Of some historical importance was the announcement by Lustgarten, in 1884, of the discovery of a bacillus but it was later shown that the organism found in the internal organs was probably the tubercle bacillus, and the one in genital chancres, the smegma bacillus.

Spirochæta Pallida or Treponema Pallidum.—In 1905 the final word on this subject was spoken by two German investigators.[1] On May 17 of that year the paper of Schaudinn and Hoffmann was read before the Berlin Medical Society. It was a model of calmness; and despite the conviction which they must have had that they had got "to the quick of the ulcer," they presented the facts quite simply and left etiological deductions to others. They had found, they said, a characteristic organism in syphilitic lesions; it was readily told from other similar forms and had been present in the primary sore of 7 cases examined, in the anal papules of 1 case, in the genital papules of 8, in 2 closed primary lesions of the skin of the penis, in inguinal buboes in 12 cases, and once in the splenic blood. Almost immediately corroboratory reports came in. By December, 1905, the *Spirochæta pallida* had been found by various observers all over the world in a great variety of syphilitic lesions. The vast amount of work subsequently done has served only to confirm these early findings both as to the presence of this spirochete in luetic lesions and as to its absence elsewhere. Further study of the group of spirochetes soon led to a change of the name of the organism to *Treponema pallidum*, which is now in general use. In Noguchi's more recent study of the spirochetes they are divided into four genera, one of which includes the treponemata. In this last genus are included, beside *Treponema pallidum*, the specific organisms of relapsing fever, of Vincent's angina, of infectious jaundice and of yaws (*Treponema pertenue*).

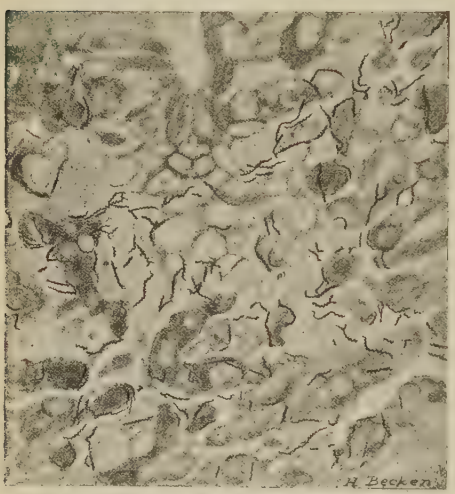
The *Treponema pallidum* (Plate IV, Fig. 1) is a long, delicate, nonrefractile, spirally curved organism. It may be seen quite well with the ordinary oil-immersion lens. Its average length is from 4 to 14 μ; smaller forms, 2 to 3 μ in length, are also seen, and organisms 20 μ long have been observed. It is pointed at both ends. Its spirals are sharp, clear cut, tight and corkscrew-like, and are less definite toward the ends than elsewhere. They vary in number from six to twenty-six, but shorter forms with only two or three curves are also seen. The length of each spiral measures from $\frac{4}{5}$ to $1\frac{2}{3}$ μ, and the large number of spirals in proportion to the length of the organism is a characteristic feature. The whole organism is usually somewhat curved; it may be S- or C-shaped, and

[1] The early articles of Schaudinn and Hoffmann appeared in the *Arbeiten aus dem Kaiserl. Gesundheitsamt*, Band xxii, Heft 2, S. 527, and in the *Deutsche med. Wchnschr.*, 1905, No. 18, S. 711.

occasionally forms a closed circle.[1] It is circular in cross-section. In both stained and fresh specimens flagella have been seen, usually one at either end, although occasionally more. The flagella are extremely delicate and are about as long as four to six spirals of the organism. The motility is of three kinds: rotation on the long axis, snaky, whip-like undulations of the whole body without locomotion, and forward and backward movements. The organism stains only faintly and with great difficulty and is believed to multiply by transverse division. It was first grown in pure culture by Noguchi in 1911.

Treponema pallidum is to be found in fairly large numbers in both smears and sections from the primary and secondary lesions; can be recovered, though much less readily, from gummata and other tertiary lesions, and has been demonstrated in the central nervous system in cases of general paresis and tabes.

Fig. 57



Section of lung, congenital syphilis. × 800.

In the fresh lesions and in the viscera of cases of congenital syphilis the organisms are often extremely numerous (Fig. 57). They have been shown to be present in the primary lesions of experimental syphilis in monkeys.

Treponema pallidum is but one member of a large group of organisms with similar morphology, and it offers therefore some difficulties in microscopic identification. The chief trouble is caused by *Treponema refringens* for this is found just where the pallidum is likely to be sought for. It occurs in the mouth, on the tonsils, in ulcerating lesions, in smegma, and on venereal warts. *Treponema pallidum* can, however, usually be recognized by its delicacy, its tinctorial obstinacy, and by the number and tight corkscrew configuration of its spirals. The refringens (Plate IV, Fig. 2), on the other hand, is larger, thicker, more refractive, and quite easily and deeply stained; but most characteristic of all are its spirals, which are broad and wavy or undulating, rather than corkscrew-shaped. Its ends are rarely pointed and are often blunt, its movements are more rapid than those of *Treponema pallidum* and it occurs in great numbers in smear specimens. Not more than two or three of Schaudinn's spirochetes, on the other hand, are usually seen in one field of a smear from a chancre, and often they are much less numerous.

Recent experimental studies of the treponema, especially by Nichols and later by Reasoner in the Army Medical School, have resulted in the

[1] This picture is probably caused by two C-shaped organisms in apposition.

finding of several strains with characteristics sufficiently distinct to furnish a means of identification and differentiation. These differential characteristics depend upon the varying reaction of the tissues of the rabbit to inoculation. The results of these studies suggest that it may eventually be shown that different strains of the syphilitic virus manifest a special predisposition to attack particular structures such as the central nervous system or the vascular system.

Modes of Transmission.—Syphilis may be either acquired or congenital. In the great majority of the *acquired* cases transmission occurs by sexual intercourse and the site of the primary lesion is the genitals; but the disease is not necessarily so transmitted. In certain regions of Russia, for example, where there are no physicians and where the most wretched hygienic conditions prevail, syphilis is, according to Tarnovsky, in 70 per cent. of the cases, transmitted by extragenital contagion. In these districts there are few prostitutes, and "rural syphilis in Russia is first and foremost syphilis of the innocent." In general, however, the primary lesion or chancre has been found to be extragenital in about 6 per cent. of all acquired cases. Such extragenital chancres may occur upon the lip, tongue, tonsil, finger, nipple or almost any other exposed part of the body. It is believed that some crack or break in the skin or mucous membranes is needed to bring about infection. The commonest site of the extragenital chancre is the lip, the infection taking place in the act of kissing. Physicians have frequently been infected on the finger or hand in examinating syphilitic patients, and obstetricians and gynecologists run a particular risk in this respect. A syphilitic infant may infect its wet nurse or a syphilitic nurse may transmit the disease to a healthy patient. While many of these extragenital infections are acquired innocently, perverted intercourse doubtless accounts for some of them. In rare instances syphilitic infection has been known to take place without the occurrence of a primary lesion (*syphilis d'emblee*). The very few trustworthy examples of this have almost all been in surgeons or nurses who have been pricked or cut during an operation.

Beside the above-mentioned modes of transmission by immediate or direct contact the disease is sometimes transmitted indirectly or by mediate contact. This may occur through the use of contaminated eating utensils, drinking cups, towels, nursing bottles, dental instruments, razors, pipes, etc. Formerly many infections occurred by the use of human virus for smallpox vaccination. Ritual circumcision and tattooing have each been responsible for the transmission of syphilis.

The highly contagious period of the disease is limited to the primary and secondary stages and it is rare that infection occurs from a patient who has had the disease for more than three or four years; but transmission of the disease has occasionally taken place in much later states and Hazen vouches for two instances in which infection occurred from a syphilitic who had had his primary lesion more than twenty years before.

Our views concerning the mode of transmission in *congenital* syphilis have undergone important changes in recent years. At present it is the general belief that syphilis is never hereditary in the true sense but that

the congenital or ante-natal cases are always due to the direct infection of the fetus by the passage of the specific organism through the placenta of the mother. According to this view transmission of the disease from the father occurs only indirectly through the infection of the mother. Women giving birth to syphilitic children are now known usually to give a positive Wassermann reaction, and even in those who fail to show a positive reaction the treponema has repeatedly been demonstrated in the maternal placenta, so that they are undoubtedly syphilitic even though they show no outward evidences of the disease.

Pathology.—Behavior of the Organism within the Body.—When implantation of the treponema has been accomplished the organism begins immediately to multiply, sets up microscopic changes in the cutaneous vessels and enters the lymph and blood-streams. By the experiments of Brown and Pearce[1] it has been shown that in animals infection of the regional lymph nodes takes within a period of less than forty-eight hours from the time of inoculation; that is, several days before either the appearance of the initial lesion or the occurrence of definite alterations in the nodes themselves. These authors showed further than the treponemata were constantly present in the circulating blood by the time the infection could be recognized at the point of inoculation. They conclude that, "for practical purposes, there is probably no appreciable time during which a syphilitic infection can be regarded as confined to the focus of entry but that, immediately infection takes place, the spirochetes begin to multiply and invade the surrounding tissues, gaining access to both the lymphatics and the blood-stream, and are widely distributed over the body even before an initial lesion can be detected." With the multiplication of the treponemata and their wide dissemination through the body there soon appears a characteristic tissue reaction, seen in the skin and mucous surfaces as the secondary eruption but probably occurring also in many of the deeper structures. It has been clearly shown by recent investigations that the central nervous system is often involved at a very early period, sometimes even before the skin eruption has appeared.

The studies of Uhlenhuth and Mulzer[2] throw an interesting light upon the question of the presence of the organisms in the circulating blood in the different states of syphilis. In 19 cases of the disease in the primary stage they found the blood infectious to rabbits in 16 (84.2 per cent.); in 36 cases of early secondary syphilis it was infectious 27 times (75 per cent.), whereas in 15 cases of late (latent) syphilis the inoculations were successful only twice.

Immunity.—Since the discovery of the specific cause of syphilis and of methods of growing the organism in pure culture and of transmitting the disease to animals, much study has been devoted to the immunological aspects of the disease in the hope that protective substances might be found which would eventually provide a rational method of prophylaxis or cure. Thus far, it must be admitted, this hope has not been realized.

[1] *Arch. of Dermat. and Syph.*, 1920, **2**, 470.
[2] *Arb. a. d. k. Gsndhtsamte*, Berlin, 1913, **44**, 307.

Although it has been shown that the sera of rabbits treated with culture organisms do contain some agglutinins for such culture organisms, efforts to produce in animals either active or passive immunity against syphilis have heretofore failed. Moreover it is becoming clearly recognized that syphilis does not confer an immunity in any way comparable to that seen in infections of bacterial origin. It is well known that with the development of the primary lesion the syphilitic patient becomes resistent to reinoculation and remains resistent throughout the whole course of the disease. Notwithstanding this, however, the invading treponemata continue to multiply in the body and to carry on their pathogenic activities, whereas in the case of most bacterial infections with the establishment of immunity the exciting organism either disappears altogether from the body or loses its pathogenic qualities.

In syphilis, moreover, with the cure of the disease the individual again becomes susceptible to infection. It is evident therefore that immunity, in the accepted meaning of that term, is not acquired in syphilis and that the resistance shown to reinoculation indicates merely that the skin and mucous membranes are in some obscure way refractory toward infection from without while they may, at the same time, react vigorously (in the form of secondary eruptions) to the spirochetes within the body. Nor can the Bordet-Wassermann reaction be looked upon as indicating the presence of protective antibodies, as this reaction is now known to be biologically non-specific.

In the light of recent knowledge the so-called laws of Colles and Profeta, which have long been considered as evidence that immunity to syphilis does occur, have lost most of their significance and importance. The former held that a mother who had borne a syphilitic child, even though she herself showed no evidence of having had the disease, could not become infected from the nursing child because of an acquired immunity to the disease. Profeta's law was to the effect that a child showing no evidence of syphilis may suckle its syphilitic mother without becoming infected thereby. It is now known that these individuals who were thought to be immune were, in fact, actually syphilitic even though they showed no manifestations of the disease. As has been said, women giving birth to syphilitic children have been shown usually to react positively to the Wassermann test and even in those who fail to show a positive reaction the treponema has frequently been found in the maternal placenta. When infection of the mother has taken place during the last few weeks of pregnancy the child may escape, not because of any immunity it possesses but because a sufficient generalization of the infection in the mother has not yet occurred.

Latent syphilis is a term which has been widely used to indicate the state of individuals known to be syphilitic who, nevertheless, show no outward manifestations of the disease. This term is very misleading and objectionable insofar as it implies that in such individuals the infection has been rendered inactive as the result of immune processes, for in many such instances it is quite certain that the organisms are continuing to excite pathological changes in some of the deeper structures, notably in the aorta and the central nervous system, even though there

be no outward signs of such activity. In other words, the condition is one of *concealed*, rather than of latent, syphilis.

There seems to be ground for believing that the existence of syphilis in a community for some length of time results in a relative immunity to it, as expressed by a lessened severity of its symptoms. This observation was strikingly made after the great European pandemic; it has been repeated since, when the disease, freshly introduced into a community and taking on a virulent form, has gradually become milder; but there is no reason to suppose that this immunity will ever become absolute and that the disease will, of itself "die out."

Pathological Anatomy.—Syphilis, which begins its pathological existence as a modest, inactive Hunterian chancre, soon enters upon a career that is unsurpassed for the variety of its manifestations. There is no organ in the body, not any tissue in the organs, which syphilis does not invade: and it is therefore manifestly difficult to speak, at least at all concisely, of the pathology; ust as it is almost impossible to describe its clinical symptoms without mentioning almost every symptom of every disease known. Certain general pathological features are, however, characteristic, and these must be described; the other more specific changes will be treated under affections of special organs. One notices throughout the pathological changes of lues the cellular infiltration and the prominent part taken by the bloodvessels, both of which features play such an important role in the chancre. Virchow called attention to the fact that all the syphilitic lesions from the chancre to the gumma are granulomata so much alike that they cannot be differentiated.

1. **The Syphiloma.**—The following are the features of the general pathological anatomy of the syphiloma as outlined by Jullien:

"(*a*) Infiltration of the derma and the mucous layers with small cells. These cells, which closely resemble the aspect of embryonic elements encountered in fleshy granulations, are heaped up at the periphery of the vessels, between the trabeculæ of the corium, and finally involve the papillæ and Malpighian bodies to such a degree that the limitation between these two layers of the skin entirely disappears.

"(*b*) The inevitable destruction of those cells which are incapable of organization. At the end of a certain time the infiltrate undergoes a fatty degeneration and enters into the organism by resorption or ends in a purulent dissolution. In any case the vitality of the secondary syphiloma is not sufficient to transform it into definite tissue. After its disappearance the elements of the tissues in the midst of which it was established again take on their normal disposition without any necessary loss of substance.

"(*c*) The centrifugal course of the neoplasm, both in its development and in its retrogression. It is always from the centre to the periphery that the infiltration takes place; the borders of the lesion are consequently more recent than the centre; hence the differences in aspect which may be presented in the two parts. When the centre becomes depressed under the influence of retrogression, the neoplasm may maintain its maximum of development at the borders; this is the reason for certain forms (cup-shaped, annular, etc.)."

The pathological changes explain the features of the various lesions. "The papule," for example, "is prominent because there is cellular infiltration; hard, because this infiltration is dense, it is brilliant, because the epidermis is tense over the summit; surrounded by a collarette, because the coloring matter of the blood furnishes an extravasation; and, finally, when resorption takes place, the epidermis wrinkles at its surface and is eliminated by an ephemeral desquamation."

2. **Cutaneous Syphilides.**—These cannot be treated in detail on account of their multitudinous varieties. The pathology of the macule, papule, and pustule will suffice as examples of the characteristic changes. The *macule* consists of an exudation of leukocytes and plasma cells about the small vessels, a proliferation of connective tissue, an infiltration of the hair, sweat, and sebaceous follicles, with round and plasma cells. Horny pigment cells are occasionally deposited in the papillæ (Ehrmann's melanoblasts). The *papule* represents a further development of the macule, due to an advance in cell proliferation toward the surface and toward the depth. Plasma cells and leukocytes occur in groups ("Zellenwucherungen"), often about the ducts of sweat glands. Round cells are numerous and giant cells frequent. Exudation of leukocytes and transudation of serum into the epidermis may occur and the papule may, therefore, be accompanied by a pustule or vesicle. The *pustule* presents a similar picture except that suppuration is present at the mouth of hair follicles or sebaceous glands. The walls of vessels, hair follicles, sebaceous and sweat glands show cellular proliferation and infiltration of cells, which reaches to the horny layer, obliterating the distinction between rete and cutis.

3. **The Gumma.**—This lesion belongs to the infectious granulomata and shows no specific elements or structure. The pathological changes are similar to those of the papule, but destructive changes are present and give the lesion its character. There is softening of the connective tissue, which is transformed into a thready, mucoid mass, consisting of detritus and cells which have undergone fatty degeneration. Lymphoid, pus, and epithelioid cells are present. At first there are no new blood-vessels formed, but later these become a feature. The overlying epidermis becomes inflamed and the upper layers of the corium swollen with a semiliquid infiltration. The gumma may be surrounded by dense, sclerotic, scar tissue, and present undeniable histological analogies with tubercle. The gumma, however, may be absorbed and finally disappear without degeneration or ulceration; this is a remarkable characteristic and is well illustrated in gumma of the testicle. The gummatous change may be diffuse, rather than confined to the limits of an infectious granuloma. The microscopic distinction between gumma and tubercle is always difficult and often impossible. In general, epithelioid cells are more frequent in tubercle, fibroblasts and connective-tissue strands in gumma; in gumma, caseation and connective-tissue proliferation are simultaneous, in tubercle the latter succeeds caseation; gummatous caseation is a much slower process than tuberculous caseation; the tubercle is often free from vessels, but new-formed vessels are a prominent feature of gumma and often persist even during necrosis. Giant cells are certainly more characteristic of tubercle than of gumma.

When the growth of the gumma ceases the younger peripheral cells become organized into connective-tissue cells, forming an envelope for the cheesy and gummatous nucleus. This envelope shrinks, the semi-fluid portions are absorbed, and finally a scar (possibly calcareous) is left behind.

4. **Lesions of the Mucous Membrane.**—When the papule occurs on mucous membranes or on moist portions of the skin it presents certain other characteristics, but remains essentially a papule. Cell proliferation invades the cutis, necrosis of the surface occurs, and a characteristic deposit is formed. This is removed mechanically and is again replaced; or the papillæ proliferate and mechanical stimulation leads to great hypertrophy, immense cauliflower condylomata resulting.

5. **Inflammation.**—Syphilis may determine inflammatory changes. Arteritis and peri-arteritis have been referred to; pharyngitis is frequent; acute nephritis is not rare; iritis and periostitis are common, and in the lungs a chronic fibroid change is sometimes seen (the fibrous interstitial pneumonia of Virchow). The non-specific inflammation of the viscera which occurs in tertiary syphilis commences as a congestion and runs a subacute or chronic course. It ends in new connective-tissue formation, cirrhosis of the organ affected, and atrophy of its parenchyma. Later the inflammation is gummatous in character.

Recent studies, notably those of Fordyce[1] and of Warthin, have emphasized anew the characteristic uniformity of the histological changes in lues throughout all its stages. "The histopathology of syphilis is a uniform one. In all stages and in all organs the lesion begins in the peri-vascular lymph spaces as a lymphocytic and plasma-cell infiltration" (Fordyce). Warthin asserts that "the essential tissue-lesion of either late or latent syphilis is an irritative or inflammatory process, usually mild in degree, characterized by lymphocytic and plasma-cell infiltrations in the stroma, particularly about the bloodvessels and lymphatics, slight tissue proliferations, eventually fibrosis, and atrophy and degeneration of the parenchyma." As a result of his histological studies of the heart and various other organs, controlled by the finding of the treponemata in sections stained by the Levaditi method, Warthin[2] believes that these microscopic changes are sufficiently characteristic and specific to establish the diagnosis of syphilis in the absence of gummata and other gross anatomical signs. The gumma, he thinks, is comparatively rare and is not the essential or typical lesion of late syphilis. In most cases, the recognition of syphilitic lesions requires a careful microscopic study of the sections, and reliance upon the well-known gross anatomical features alone for the postmortem diagnosis of the disease will result in failure to recognize many cases. The discrepancy between the autopsy statistics of Symmers and of himself is to be thus explained, he thinks.

The specific inflammatory lesions due to localization of the treponemata are found in the heart, aorta, pulmonary and other large arteries, central nervous system, liver, pancreas, adrenals, testicle, prostate, prevertebral and mesenteric tissues. In some instances these lesions are only minute

[1] *Am. Jour. Med. Sci.*, 1915, **149**, 761.
[2] *Loc. cit.*

collections of a few cells, in others they are larger infiltrations visible to the naked eye. Often the treponemata can be demonstrated in immediate proximity to these lesions. In every case of syphilis examined Warthin found the heart muscle invaded, the essential change being an interstitial myocarditis marked by infiltrations of lymphocytes and plasma-cells along the vessels between the muscle fibres.

These far-reaching conclusions of Warthin have not yet won general acceptance among pathologists. There is still some question as to whether such microscopic lesions are sufficiently characteristic and specific to warrant the diagnosis of syphilis in the absence of demonstrable treponemata or of other characteristic lesions of the disease. Confirmation of Warthin's views would revolutionize our present conception not only of the pathological anatomy of syphilis but of the incidence of the disease as well.

6. **Blood.**—The blood picture, which is never characteristic, may show various grades of anemia. A normal count, although unusual, occurs. A severe chlorotic anemia is the rule in the primary stage and is most marked in women. With the appearance of the rash there is further diminution in the hemoglobin; the red blood count may remain about the same or drop very rapidly. In tertiary and congenital syphilis the picture may be that of primary pernicious anemia with numerous megaloblasts; normoblasts, gigantoblasts, microcytes, and poikilocytes also are seen. Mercurial treatment causes the red cells to rise, although its *first* effect is often a drop, accompanied, in some cases, by hemoglobinuria. Sometimes a hypercythemia results from the treatment; but if it be continued too long or in too large doses, mercury itself may cause an anemia. A large inunction or injection of mercury, given after the disease has ceased to be local and has invaded the lymph glands, causes an immediate drop of from 10 to 20 per cent. in hemoglobin, which rises, in a few days, to normal or above normal. This is known as Justus' test; it may be obtained in any case of florid lues, is not present during the early primary stage, and, while not certainly pathognomonic, is valuable.

The leukocytes are normal in the primary stage, or slightly increased. If mercury be given, the percentage of polymorphonuclear neutrophiles increases. During the secondaries there is slight leukocytosis, with increased lymphocytes and eosinophiles. The severe anemia of the tertiary stage is often accompanied by leukocytosis with high lymphocytosis, and myelocytes occur in severe cases.

7. **Amyloid Degeneration.** Syphilis plays an important role in the etiology of amyloid degeneration; 21 per cent. of 80 cases of amyloid degeneration studied by Hoffmann in the Berlin Pathological Institute were due to syphilis. The intestines, liver, spleen, and kidneys are oftenest involved; and the condition is common in association with rectal lues in women. It is rare in the congenital form.

Clinical Features.—Three clinical stages in the course of a typical case of syphilis were recognized by Ricord, and to these others have added a fourth. The primary is the stage of the chancre; the secondary is the stage of the acute general invasion of the virus; the tertiary is the

stage of the late, relatively non-virulent, localized manifestations, and the quaternary is the stage of what were termed parasyphilitic phenomena. The division is, of course, more or less an academic one; no disease, syphilis least of all, follows any rule in its clinical phenomena. Nor is the evolution of the disease so constant or orderly an affair as this classification might suggest. One of the stages may be entirely absent; the secondary and tertiary stages may be separated by long intervals or be almost simultaneous, and almost any variation may be observed. On the average it represents an approximation to the truth; and while its limitations must be constantly kept in mind, its value both in clinical observation and in facilitating description cannot be questioned.

The Chancre.—Syphilis makes its debut in the guise of the Hunterian or hard chancre which appears as a rule within the first three weeks after infection, rarely earlier than the tenth day. Attention is sometimes first called to the lesion, as Hunter observed, by an itching in the affected part; but the sore, both at its onset and later, is usually quite painless and free from sensitiveness on pressure. Its very early appearance varies greatly and at this time diagnosis is often quite impossible. "In the early part of my life," wrote Colles, "I thought I could tell what was a chancre; but I am now convinced that a primary venereal ulcer may *begin* in any one possible form of an ulcer." Usually it is a small papule which is first noticed. As the sore develops, however, it takes on more or less diagnostic characteristics. It forms a brownish-red, firm, often button-like nodule with a shallow surface depression. Its size, shape, and consistency vary greatly; but characteristically it is circular or oval, measures 1 x 1.5 cm., and is quite hard. Its edges are sharply defined and the induration about it does not, as is usual in other inflammations, extend far beyond the limits of the lesion itself, but terminates abruptly. Its extreme mobility is a characteristic feature. At this stage the chancre is really an exulceration resting on an indurated base. The surface of the base is regular, brilliant red (much the color of muscle) and on a level with the surrounding tissues or slightly above them. Its centre is not infrequently grayish or diphtheroid. The secretion is scanty and thin, and suppuration does not usually occur. If the lesion is on a mucous membrane, the surface remains moist and glistening; but in chancre of the skin the secretion often dries and forms crusts. Secretion may, however, be altogether absent. The induration, which may feel like parchment, is usually more resistant and elastic, resembling cartilage. The sore is typically single, *but in about one-fourth of the cases it is multiple;* Fournier reported a patient exhibiting twenty-six simultaneous initial lesions.

The chancre is usually accompanied by no general constitutional disturbances. Involvement of the neighboring lymph channels, particularly along the dorsum of the penis, is seen, but it is not associated with inflammatory redness. Soon after the appearance of the chancre the neighboring lymph glands become enlarged, forming, when the sore is a genital one, the characteristic luetic inguinal buboes, most frequently seen in both groins. They remain discrete, are hard, free from tenderness, and do not suppurate. They survive the chancre and become,

later, part of the general adenopathy of the secondary stage. Enlarged inguinal glands are occasionally entirely absent.

Complications.—1. The chancre is sometimes accompanied by marked inflammatory reaction. This often takes the form of intense œdema and phimosis. A condition of elephantiasis may be present and gangrene is occasionally seen.

2. Not infrequently the chancre becomes phagedenic. This is most often seen in old men and in diabetic or otherwise diseased patients.

3. The Hunterian chancre may be accompanied by a soft chancre, and this mixed infection is not infrequent. Very often, too, the evolution of a soft chancre into a hard one is observed. This is due to a mixed original inoculation; the soft sore, with a short incubation period, appears first, its base becomes gradually indurated and soon takes on the typical Hunterian characteristics (mixed chancre).

Site.—Chancres may be either genital or extragenital. The characteristics of the lesion vary with its site, and induration is usually less marked in chancres of the skin than of the glans, and in women than in men.

The primary lesion is usually situated on the genitals. In men it is most frequently seen, as Hunter observed, on the frenum and coronal sulcus; but the glans, the urethra (as far as the fossa navicularis), the dorsum of the penis, and the scrotum are occasionally the site of chancre. In women it may occur anywhere on the external genitalia, and even in the cervical canal itself. Perigenital chancres are seen on the mons veneris, the inner surface of the thighs, and the perineum.

The sites of extragenital chancres have been discussed. Such lesions are apt to be of rather larger size than genital chancres but in general present the same characteristics.

Varieties.—Chancres vary as to the extent and form of ulceration (simple fissures, small ulcers, giant ulcers), the depth of ulceration (erosive, ulcerative, and boring chancres), the characters of the surface (papular, squamous, diphtheroid, pustular, and papillomatous chancres), and the character of the base (foliaceous, parchment, hypertrophic, elevated, and elephantiac chancres).

Course.—With the appearance of the eruption retrogressive changes in the chancre itself usually begin; they may set in earlier or be much delayed. The induration diminishes, the central portions of the chancre undergo fatty or ulcerative degeneration, and finally the sore disappears. Absolutely no trace of the lesion whatever may be left behind, particularly if it be situated on a mucous surface. As a rule an indurated scar persists and may last for years; not infrequently the scar is pigmented. If the sore becomes infected or assumes a phagedenic character its clinical course is obviously altered. Prognosis as to the severity of the syphilis is by no means to be made from the character of the sore.

Diagnosis.—The sharply defined borders, the induration, the slight sensitiveness, the scanty, non-purulent secretion, and the motility are the typical clinical features of the Hunterian chancre; but no one of them is invariable and the diagnosis of the sore is usually difficult, very often impossible, and, as a rule, not to be made, aside from finding the

Treponema pallidum microscopically, until sufficient time has elapsed for the appearance of secondary symptoms. The chancroidal ulcer and the lesions of herpes progenitalis offer the greatest difficulties in diagnosis of genital chancre. Other genital lesions which may be confused with chancre are ulcerating secondary syphilides, suppurative folliculitis, erosive balanitis and vulvitis, and certain of the tertiary syphilitic lesions. The appearance of these is, however, usually not typical of Hunterian chancre; the history is often helpful; and microscopic examination of smears will eliminate the non-luetic lesions.

One can hardly overemphasize the importance of keeping a patient with a genital sore under observation, for it is very difficult indeed, positively, to exclude syphilis in some cases. Many of the diagnostic rules are fallacious; the idea, for instance, that chancroidal lesions are always multiple, luetic lesions always single, has led many astray. Little value can be attached to the history in these cases and therefore the incubation period of the sore cannot often be determined with accuracy. Nor does the absence of induration exclude chancre.

The most trustworthy means of diagnosis is the finding of the *Treponema pallidum* in the secretion of the sore, with the aid of dark-field illumination. At this stage the Wassermann reaction is usually not positive. Craig's statistics[1] show that during the first week of the chancre only 27.6 per cent. of the cases responded positively, but that the percentage increased rapidly thereafter until in the fifth week a positive reaction was obtained in 79.4 per cent.

The diagnosis of *extragenital* chancres offers greater difficulties. Here the position of the lesion instead of attracting attention immediately to syphilis may throw one off guard. The characteristics of the Hunterian sore are, however, usually to be found, and one should look particularly for the accompanying adenopathy. Chancres of the skin may be mistaken for pustular ecthyma and for tuberculous ulcerations. In the pharynx one may suspect diphtheria; on the fingers, lips, tongue, and tonsil differentiation from carcinoma is often difficult. Extragenital chancres may also resemble ordinary inflammations (*e. g.*, panaritium, abscess of the tonsil, etc.).

The Secondary Stage.—The initial lesion is the clinical expression of syphilis in its primary and localized form. Although we now know that almost immediately after infection occurs the organisms begin to multiply and that they soon become widely disseminated through the body, it is, nevertheless, true that during the first few weeks of the disease (the so-called second incubation period) no manifestations other than the local one are to be observed. After a lapse of about four to eight weeks from the appearance of the chancre the manifestations of the disease change from local to general ones; constitutional signs and symptoms, in great variety, appear; and their appearance marks the onset of the secondary stage. To this stage no terminal limit can be set; sometimes it lasts a few weeks, at other times many months; its course is greatly influenced by treatment; and if the disease is not well treated it may either

[1] Bull. No. 3, *U. S. War Dept. Office of Surg. Gen.*, 1913.

pass directly into the tertiary form or disappear entirely, to reappear, after the lapse of months or years, as tertiary syphilis.

The symptoms of secondary syphilis are in a general way those of a more or less grave acute infection; but a larger and motley group of specific symptoms is also superadded. The most characteristic of the latter are the lesions of the skin and mucous membranes; these are also quite often the most apparent manifestations as well as the first to appear.

1. *Symptoms of an Acute General Infection. General constitutional disturbances* are usually present, often marked and in striking contrast to the feeling of well-being during the primary stage. There is loss of weight and strength; the patients feel badly, and this condition may be exaggerated by anxiety over the disease. The appetite becomes poor, extreme anorexia being occasionally observed. In nervous women, however, bulimia is sometimes seen. *Headache* is a frequent, characteristic, and troublesome symptom. Usually it is described as a deep heaviness present most of the time, but much worse in the evening. Sometimes it is violent, almost intolerable, and quite prevents participation in the activities of life. The *tonsils* are often swollen independently of the occurrence of mucous patches. *Sore throat* is frequently complained of (angina erythematosa syphilitica). When the angina spreads to the uvula and soft palate the picture is characteristic and almost pathognomonic. The inflamed area itself is dark crimson, and is abruptly separated from the healthy mucosa anteriorly by an absolutely sharp border. The lingual tonsils may be swollen and dysphagia result. The *spleen* is sometimes enlarged, and this fact, if fever and roseola suggest typhoid fever, may add confusion to the diagnosis. Occasionally *jaundice* is present. Albuminuria is not frequent, but a form of *nephritis* occurs, which will be discussed under Visceral Lesions. *Anemia* is a feature of the secondary stage; it is usually of the chlorotic type and may be attended by definite clinical symptoms (cardiac palpitation, sense of oppression, etc.). In neurotic individuals syphilis often causes an extreme exaggeration of the symptoms previously present. Intense psychic depression is not rare; pains in the limbs and analgesias and anesthesias (particularly of the breasts in females) are seen, and sometimes the patients suffer from definite convulsive attacks. The patellar reflex may be abolished.

Enlargement of the lymphatic glands is one of the characteristic features of secondary syphilis. It is not a local affair but an expression of general infection. The glands are not large, are indolent, painless, hard, discrete, unaccompanied by neighboring lymphangitis, and do not suppurate. The intensity of the adenitis is not proportional to the severity of the disease; on the contrary, marked glandular swelling usually accompanies mild lues, and *vice versa*. The most frequent lymphatic glands to be involved, arranged in order of predilection, are the postcervical, the sternomastoid, the submaxillary, the epitrochlear, the axillary, and the inguinal. Enlargement of the epitrochlears is particularly suggestive, since its involvement in other conditions is not very frequent. Involvement of a small gland just under the outer border of the pectoralis major has been considered almost pathognomonic of lues; the gland is certainly

rarely involved in acute infectious processes, since it lies off the drainage tract of parts oftenest so affected. Occasionally such an enlarged gland after removal is found to be tuberculous. Enlargement of the inguinal glands is of little diagnostic value; it is by no means always seen in syphilis, and is common in other conditions. Palpable and even enlarged lymphatic glands in this region are almost a constant finding in patients in a genito-urinary out-patient clinic, and Dietrich found that of 499 healthy individuals 99 per cent. showed enlarged lymph glands somewhere in the body.

Fever.—Fever is a frequent phenomenon of the secondary stage and is one of the features of its resemblance to an acute infectious disease. At the end of the fifteenth and during the early years of the sixteenth centuries, when syphilis assumed epidemic proportions, it was compared with smallpox (owing probably to the intensity and persistence of the cutaneous features), and hence the name variola magna, the great pox, or *the* pox. The frequency of fever during the course of syphilis is variously estimated. A large majority of cases have a slight elevation of temperature in the period of incubation. Throughout its course the disease may be afebrile, and patients with the most extensive lesions may have normal temperature.

The fever occurs at three periods—preliminary, stage of invasion, and at any time during the tertiary lesions:

1. *Preliminary Fever.*—During the period of incubation the patient may be without symptoms, but there may be a feeling of weakness and loss of appetite, with pallor. In a few instances at this period fever occurs. It may be ushered in by a chill (Lang) and be accompanied by headache, nausea, and pains in the limbs.

2. *Fever of Invasion.*—As a rule, by the time we see the patient in the hospital the fever has disappeared. Various estimates give the proportion of cases with fever at from 25 to 35 per cent. It is probable if we had accurate measurements, that slight fever would be found in a much larger proportion. It may antedate the eruption by a week or two and may set in abruptly with a chill. It is commonly associated with headache, malaise, and a furred tongue. The type of fever is usually remittent. Where malaria prevails the case may be confounded with the estivo-autumnal type of this disease. Much less frequently the fever of invasion is frankly intermittent. No case of this type at this period of the disease has come under our observation, but Fournier refers to it. The pains in the limbs and about the joints, with the slight fever, may lead to the diagnosis of rheumatic fever. At this stage the picture may occasionally simulate typhoid fever; Fournier describes the condition as "*typhose syphilitique.*"

3. *Fever of the Tertiary Lesions.*—It is particularly at this period that fever may lead to serious errors in diagnosis. The profession scarcely realizes that protracted fever of almost any type may occur in tertiary syphilis. It is probable that many of the cases of obscure, unclassifiable fevers which are described from time to time are due to syphilitic lesions. A man may have quite extensive gummatous disease of the liver without pain or without great enlargement. On the other hand, there can be

no question that the most extensive tertiary lesions may be present with a normal or with a very slight elevation of temperature. Among diseases for which the fever is apt to be mistaken are:

Rheumatic Fever.—Nodes growing close to joints may cause periarticular enlargement with pain, and if fever be present the case may be regarded as one of rheumatic fever.

Malaria.—It seems scarcely possible that the two diseases should be mistaken, and yet in the case reported by Sydney Philips there were ague-like chills and the temperature curve was most suggestive. In one of our cases, reported by Futcher, a physician, aged fifty-nine years, had chills and fever which he himself regarded as malarial (though quinine had had no effect on the condition). When stripped, the diagnosis was easy, as the patient had a rupia-like eruption and tender nodes on the shoulders and sternum.

Typhoid Fever.—Cases have been reported in which the syphilitic fever has been mistaken for typhoid. They are rare, however, as J. D. Rolleston states that out of a total of 3076 cases admitted to the London Fever Hospitals wrongly certified to be typhoid fever, only 10 were found to have syphilis. For weeks the following case, reported in Futcher's paper, was suspected to be typhoid fever. The patient, aged thirty-nine years, had had irregular fever for three weeks previous to admission. The temperature chart here annexed (Fig. 58) shows an intermittent and remittent fever from August 8 until September 16. There were no malarial parasites. The spleen was enlarged. A continuous fever of this character in the autumn which resisted quinine was naturally regarded as typhoid. It was not until September 12 that suspicion was aroused and W. S. Thayer noted the presence of thickening of the clavicles from old nodes. There was a definite scar on the glans and the patient acknowledged infection. Potassium iodide was given and by September 16 the temperature was normal.

Tuberculosis.—Perhaps more important than any of these is the simulation of pulmonary tuberculosis by syphilitic fever. Many writers have called attention to these cases, and E. G. Janeway brought a series before the Association of American Physicians in 1898. The question of the relation of the two diseases has been considered in a monograph by Sergent.[1] It is more particularly in the form in which there are sweats, irregular fever, and loss of weight, associated with a slight cough, that tuberculosis is suspected. The absence of well-marked physical signs and of bacilli in the sputum may call attention to the anomalous nature of a case. The liver is very often enlarged, irregular, and tender, and it is this feature that may suggest the proper treatment.

It is by no means easy to see why fever is present in some cases of syphilis and absent in others. In many instances the liver is involved, and it has been suggested that the damage to this organ is sufficient to prevent its proper action as a filter, and in consequence fever-producing substances reach the general circulation. In a few cases gummata become secondarily infected by pyogenic organisms, but this is exceed-

[1] *Syphilis et tuberculose*, Paris, 1907.

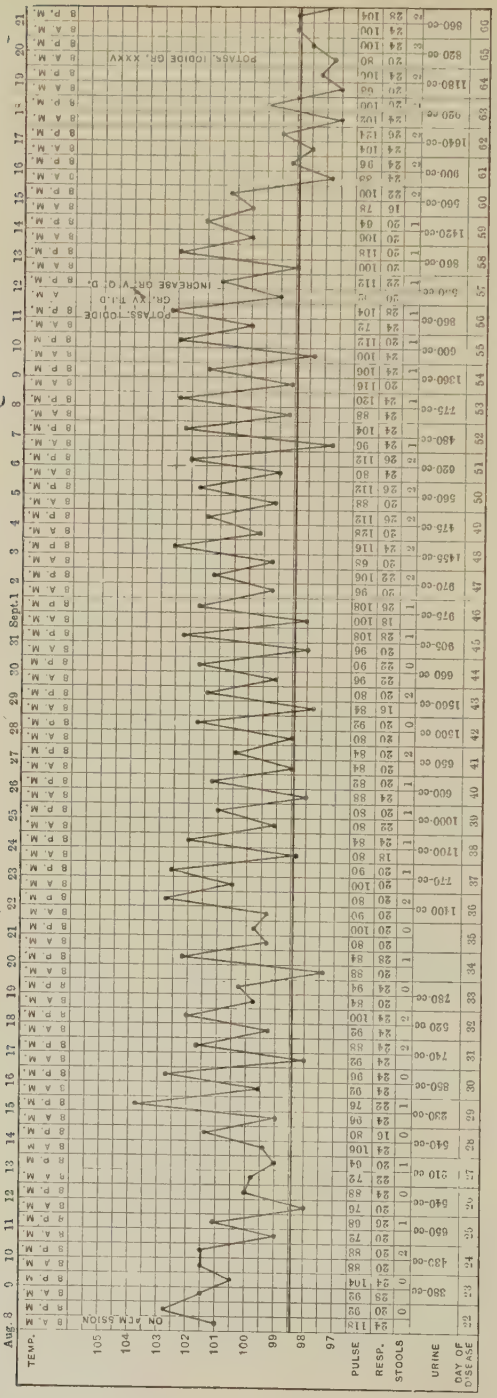


FIG. 58

Fever curve suggesting typhoid fever.

ingly rare. A number of interesting examples of protracted fever of hectic type in tertiary syphilis has been recorded by Thayer.[1]

2. *Specific Symptoms of Secondary Syphilis.*—*Syphilitic arthritis* is not very infrequent and usually takes the form of dull pains in the joints of the extremities much like the "growing pains" of children, or of "rheumatism;" it is frequently regarded by the laity as rheumatic in character. The joints are usually not swollen, tender or red, although a small effusion may be present. The pains are, as a rule, not severe, but are worse at night and may be intense. They persist for a longer or shorter period, then disappear without apparent cause, and often return at irregular intervals. They resist all measures except specific treatment. More characteristic still are the pains in the periosteum of the long bones; the clavicle, sternum, tibia, and humerus are most frequently affected. When the bones of the head are involved, dull, remittent headaches occur. These pains are usually worse at night and are out of all proportion to objective signs; the latter are, as a rule, absent, although there may be swelling of the periosteum and even a definite periostitis. The muscles and joints are often stiff and sore.

Ocular symptoms are often present. The most frequent of these is iritis. At first only one eye but finally both are involved. The iritis may be plastic, serous, or gummatous. The third form alone is peculiar to lues. It is accompanied by all the signs and symptoms of ordinary iritis. In addition one or more yellowish or yellowish-red, nodular elevations are seen, varying in size from a hemp-seed to a small pea. They are situated in the pupillary margin, on the ciliary border or between the two, but they tend to coalesce. The prognosis is doubtful on account of the frequent formation of posterior synechiæ.

Disturbances of the nervous system are frequent and of the gravest import. They are sometimes responsible for death during the secondary stage. Their full treatment belongs to neurology and they will be dealt with subsequently. The most serious involvements are due to the characteristic acute arteritis, thrombosis of the cerebral arteries with softening being a not infrequent occurrence. Actual rupture of a syphilitic artery (the frequent cause of apoplexy in the young) is usually a phenomenon of the tertiary stage, and is due to a gummatous change in the vessel wall. Acute meningomyelitis, peripheral neuritides, and compression paralysis due to periosteal lesions are fairly common.

Functional disturbances are not uncommon. Fenger and others have shown that the skin and tendon reflexes are first increased and then depressed, sometimes finally disappearing.

Visceral lesions are so much more characteristic of tertiary lues than of secondary that they are described together. There are, however, sundry symptoms occurring in the secondary stage, which are undoubtedly due to some pathological change in the viscera and which may run imperceptibly into the tertiary symptoms which arise from gummatous inflammations. The bone symptoms are an example. In addition to the pains already described, a periostitis with the appearance of painful

[1] *International Clinics*, 1923, **4**, series 33.

and tender nodules is not uncommon; and an osteitis with the formation of exostoses is occasionally seen, particularly in the tibia. So, too, there may be arthritis with effusion, which may even be polyarticular and resemble rheumatic fever. Serous exudation is also seen occasionally in the tendons and bursæ. The involvement of the liver in some pathological change is probably to be inferred from the jaundice which sometimes appears early.

Cutaneous and mucous lesions are the most characteristic and constant manifestations of secondary syphilis. Nowhere is the wanton nature of the disease more obvious than in its skin lesions; for there is hardly a cutaneous affection which lues may not simulate. The cutaneous lesions, however, have certain common characteristics which distinguish them in part or in whole from other skin diseases. These are as follows:

(*a*) The syphilitic lesions are usually circular or approximately so.

(*b*) Their evolution is slow and the successive crops of eruption are dissimilar.

(*c*) They are more or less symmetrical in their distribution, showing a tendency to grouping, particularly in circles and semicircles.

(*d*) They have a characteristic reddish-copper color, which resembles raw ham.

(*e*) They are usually indurated and often present at the periphery a raised collarette (the *collarette* of Biett).

(*f*) They usually cause no itching or other subjective symptoms, although in occasional cases pain is marked.

(*g*) They tend to resolve, although often leaving behind them scars, not infrequently pigmented. (In the precocious, malignant syphilide, rapid ulceration with extensive tissue destruction occurs.)

(*h*) They tend to become generalized and to involve large areas of skin. When localized, they have certain seats of predilection—the forehead (corona veneris), the extremities, the anogenital region, etc. The dorsal surfaces of the hands, wrists, and feet are exempt, and the sternal and clavicular regions are rarely involved except in the late destructive lesions.

(*i*) The scales are thinner, more superficial and less abundant than those in non-luetic lesions; they are dirty gray and do not glisten.

(*j*) The crusts are gray, greenish brown, or black; they are made up of superimposed layers; the surfaces are rough and laminated, and they are more easily detached and thicker than in non-syphilitic lesions.

(*k*) The ulcerations tend to be kidney- or horseshoe-shaped.

(*l*) The lesions are altered by climate, age, sex, alcoholism, and the presence of so-called "diatheses." This is particularly marked in seborrhœic individuals, in whom the luetic eruptions often take on seborrhœic characteristics (the "interlocking of seborrhœa and lues" of Unna). This characteristic is known as syphilitic imitation.

(*m*) Finally, they are polymorphous, often manifesting themselves simultaneously in various forms.

The most frequent lesions are:

1. *Syphilitic Roseola.*—The secondary stage is oftenest inaugurated by the appearance of a measly, roseolous rash, and this event may be

said to end the second incubation period. It takes place about the forty-fifth day after the appearance of the chancre. The rash usually appears first on the flanks and the sides of the thorax; thence it extends to the trunk and the extensor surfaces of the limbs. The face and hands are, as a rule, not involved. The rash consists of small, flat, usually round or oval macular spots. They are all of about the same size and are widely disseminated. At first they are rose-colored, later becoming darker, wine-colored, and finally fading into a pinkish yellow. Pressure makes them disappear only in the early stages. If observed through blue glass, as advised by Broca, the macules always become more apparent, and they may be recognized in this way when not otherwise visible. Occasionally the lesions are somewhat raised, like the wheals of urticaria. The rash comes out slowly; it then persists for several weeks and finally gradually disappears. In some cases its whole course is a rapid one. Recurrences are not infrequent, and luetic patients may exhibit repeated macular eruptions at intervals even of years.

The *diagnosis* of syphilitic roseola from other macular cutaneous affections sometimes presents a good deal of difficulty. Measles and pityriasis rosea are the two diseases most frequently to be differentiated. As a rule, the history, the nature of the accompanying constitutional and other disturbances, and careful examination of the lesions for specific luetic characteristics will make the diagnosis. The frequent involvement of the face in the rash of measles and its rare involvement in syphilis is an important point in the diagnosis. Other acute exanthemata, medicinal rashes, the eruptions of typhus and typhoid, erythema, and the roseola of gonorrhœa may also be mistaken for the macular syphilide.

2. *The Papular Eruption.*—This represents the second state in the evolution of the cutaneous syphilide. It usually follows the roseola by a short interval, but in some instances it comes out before the latter has disappeared or its appearance may be much delayed. The eruption consists of round, or nearly round, reddish, raised papules, varying in size from a lentil to a ten-cent piece. The lesions may be quite intact, but are often covered with a slightly squamous epidermis. They are situated most often on the trunk and face. Not infrequently they lie arranged in groups around a central element (syphilide papuleuse en corymbes of the French). The miliary or lichenoid form of papule deserves special description. When appearing early the lesions are very numerous and usually uniformly distributed; the abdomen, back, limbs, and face may be covered.

In its *late form*, the papular syphilide appears generally three or four months after the onset of the disease and the lesions are much less numerous. It is a polymorphous eruption, but the lesions are in general miliary and of a reddish-brown color. They are not infrequently capped by a small pustule, or covered with a crust or a scale. They are arranged in groups, often like constellations. Another more special form of papular syphilide often seen and of great interest from a diagnostic standpoint is the badly named syphilitic psoriasis. Here the lesion is a large copper- or ham-colored one, occupying a large extent of body surface (face or limbs). The edges are often indistinct, and the lesion consists

of numerous concentric circles. On the surface the epidermis is partly detached in the form of dirty, dry scales, which may be easily removed without bleeding. Fissures and rhagades often accompany this syphilide, and its resemblance to ordinary psoriasis is obvious; but the localization, the rapid evolution, the influence of specific treatment and the appearance of the scales, together with the general clinical features of the case, are usually sufficient to make the diagnosis.

The *large papular* or *lenticular* syphilide is quite commonly seen. It shows a predilection for sites about the natural orifices of the body; but is also seen on the neck, trunk, chin, and palms. It may appear at any time in the secondary stage and be the only cutaneous manifestation. Often it occurs simultaneously with the mucous patches. The lenticular papule is the most common and characteristic of the papular eruptions. The lesions are round or oval, with sharp borders and slight elevation. At first they are small and red, but later become copper-colored. The surface becomes shiny, the lesion breaks at its centre and desquamates. The desquamation is repeated until finally the lesions disappear, leaving behind them brownish or bluish-gray spots. The eruption usually starts on the forehead (corona veneris) or the nape of the neck; it then spreads to the abdomen and in two weeks is pretty well generalized. It comes out in crops and may last for ten months.

The papular rash sometimes becomes *nummular*. Here the lesions are large, with marked umbilication and a tendency to desquamation. Later they become annular, with a ring-shaped periphery of induration persisting. Intersection and interfusion of such circular, semicircular, and elliptical patches give a dreadful and bizarre appearance.

The secondary papular syphiloderm of the palms and soles (psoriasis palmaris et plantaris syphilitica) appears as lentil-sized, non-elevated, brownish spots, which are indurated and evolve slowly. When retrogressive changes begin, a white, glistening scale forms at the centre, surmounting a smooth, reddish depression. A collar of semidetached scales forms around the papule and a brown stain is left after the disappearance of the lesion. Fissures and ulcerations are not uncommon. The syphilide is chronic in its course, obstinate to treatment, and frequently relapses. It is pathognomonic of lues, but must be distinguished from eczema and, rarely, from psoriasis.

The moist papule or broad *condyloma* occurs where the lesion is exposed to warmth or maceration. Neglect and uncleanliness favor its development. It appears as a flat, button-like excrescence, often much elevated above the surrounding skin; its surface may be papillary, is denuded of epithelium, and covered by a layer of dirty, grayish material, which is usually bathed in a foul, thin secretion. Condylomata are much commoner in women than in men. The lesions are most often bilateral and are extremely infectious. They hypertrophy, particularly when neglected, and may then coalesce, forming extensive, flattened, mushroom excrescences. Condylomata occur most often about the anus, but they are also frequently seen on the vulva, perineum, scrotum, thigh, etc. They are very liable to recur frequently. The diagnosis is, as a rule, easy.

3. *The Vesicular Syphilide.*- This form is excessively rare and is ephemeral when it occurs at all, being soon replaced by crusts. Small vesicles are sometimes seen in connection with the miliary papule. It is doubtful if true bullæ ever occur.

4. The *pustular syphilide* is, on the whole, rare in the secondary stage, and its occurrence then usually indicates a severe type of the disease. It occurs most often in cachectic or debilitated subjects. It is the latest of the secondary eruptions, is obstinate to treatment and prone to relapse. The pustules vary in size from small acuminated, acne-like lesions to large, pustulo-crustaceous forms. Syphilitic polymorphism is well exhibited by the pustular syphilide, the lesions varying in size, number, distribution, and extent of suppuration. The lesion may resemble any of the pustular skin diseases (acne, ecthyma, varicella, impetigo, etc.); but two clinical forms, the small and the large pustular syphiloderm, should be recognized.

The *small pustular* syphiloderm resembles acne in many respects. The lesions, which develop from papules, are small, grow slowly, and often remain stationary for weeks, drying up finally into yellow crusts. In the early form the pustules are very numerous and are well scattered over the body. In the later forms they tend to be grouped on the scalp, elbows, knees, etc. Successive crops of small pustules often follow one another for months. In the diagnosis the distinction from acne, variola, and varicella offers the chief difficulty.

The *large pustular* syphiloderm begins as the large lenticular papule, which rapidly becomes pustular; the pustule soon ruptures or dries up into a crust, removal of which shows an ulceration beneath. When the ulceration heals a brown, pigmented scar is left behind. The lesion, however, usually lasts for a long while; the crusts heaping up to form the rupia syphilitica. This rupial eruption is frequent and striking. It begins as a flat papule, which becomes bullous or purulent, and is surrounded by a livid inflammatory areola. The pustule ruptures and the contents dry into brown or black crusts under which ulceration continues. The crusts, in this way, become stratified and thickened (oyster-shell appearance). The base increases in size and the lesion in height, becoming finally cone-shaped. If the crusts are removed an indolent ulcer is exposed with abrupt, undermined edges, and containing serosanguineous pus. The diagnosis between the large pustular syphiloderm and variola is sometimes very difficult. The syphiloderm, however, makes its appearance more slowly, begins upon the trunk and not upon the face, and shows the concomitant signs of lues.

It is not certain whether the pustular syphilide is the result of an actual secondary invasion or not. Unna has shown that such an invasion is very rarely demonstrable.

5. The *tuberculous* and *ulcerated syphilide* merges into the papular syphiloderm on the one hand and the gumma on the other. It does not usually appear until about two years after the initial sore. When occurring early it signifies a grave form of the disease. The lesions are circumscribed, brownish-red, bean- to walnut-sized infiltrated tumors, usually relatively few in number and tending to be grouped, particularly upon the nose and forehead. The course is chronic, the lesions disappearing

by absorption or ulceration. When the lesions are few and on the face the similarity to lupus vulgaris may be very striking.

The ulcerated syphilide is either the subsequent stage of the tuberculous syphilide or appears as a manifestation of the rapid malignant form of syphilis. The lesions appear as red, brownish tubercles, which soon soften and ulcerate. There is an irregular loss of substance, with suppuration. This may be extensive, causing great deformity. If the lesion heals, it persists for a while as a reddish infiltration, with a protruding border and covered by a crust. It may be 3 or 4 cm. in diameter. When it disappears it leaves behind it a marked scar, often with a surrounding area of pigment. The lesion may be situated anywhere on the body, but is most often on the legs. It occurs most frequently in weak subjects and may follow the chancre immediately.

6. *Pigmented Syphilide.*—This cutaneous lesion appears six to twenty-six months after the chancre; it is unique among the cutaneous syphilides in its resistance to specific treatment; it is accompanied by no symptoms and is sometimes regarded as a parasyphilitic manifestation. It is more frequent in young patients and in women than in men. It is called by German writers syphilitic leukoderma and consists of large, non-elevated, confluent, grayish patches enclosing circular or oval areas of normal skin among them. The general arrangement suggests lace with large meshes. The non-colored portions of skin appear, by contrast, whiter than normal skin. The rash is almost always situated on the sides of the neck and is symmetrically disposed; it is also seen in front of the axillæ, on the sides of the abdomen, and on the flanks. Occasionally it occurs on the entire body. It often occurs without having been preceded by any other eruption. Its pathology is not clear; Unna and the French consider the pigmented syphilide as a primary cutaneous manifestation of the disease; the Germans regard it as the remains of an old eruption.

7. *Changes in the Hair and Nails.*—*Alopecia* is a frequent and well-known, although by no means constant, sign of secondary syphilis. It appears during the third or fourth months of the disease, and may be either general or circumscribed (alopecia alveolaris). At first single hairs fall out; later spots of alopecia, varying in size from a lentil to a silver dollar, gradually appear. There are no broken hairs in the spots—an important fact for diagnosis. The alopecia often occurs simultaneously with the pigmented syphilide of the neck. The eyebrows at the same time may be affected and sometimes fall out entirely. The hair is reproduced after syphilitic alopecia and the prognosis is, therefore, almost invariably good. The fall of the hair is due to a folliculitis of the hair follicles; it is accompanied by decoloration of the deep portions of the hair and by a dilatation of the small vessels about the follicles. Changes in the nails are not infrequent. The *nails* may be cracked or hypertrophied; and often there is an accompanying involvement of the periungual tissues (syphilitic onychia and paronychia).

8. *Lesions of the Mucous Membranes.*—These are among the most important and constant manifestations. On account of their extreme virulence they are a grave feature in the spread of the disease. All the lesions seen on the skin may also occur on the mucous membranes; but

the most characteristic lesion is the well-known *mucous patch*. This is seen oftenest in the mouth and consists of a reddish or characteristically opal, slightly raised, papular area, topped by a small erosion. It occurs at various places in the buccal cavity, quite often on the tonsils; and is seen oftenest in mouths subject to some irritation like that of tobacco. When the mucous patch occurs on a site subject to mechanical irritation and to neglect (on the vulva, about the anus, etc.) its character changes and it is called a condyloma. It becomes larger, protrudes, is covered by fungous, papillomatous growths, and has an abundant, foul secretion. This may ulcerate and become diphtheroid. Mucous patches often recur many times.

The mucous patches may become confluent and cover large areas. Rhagades and painful fissures are often associated with them. They may cause marked subjective symptoms. Mucous patches are to be diagnosed from mercurial stomatitis, leukoplakia buccalis, and aphthous erosions. Their frequent occurrence on the tonsils and soft palate is an important point in diagnosis.

The macular, papular, and even pustular syphilides may be situated in the mouth. The *angina syphilitica*, of greatest interest on account of its clinical importance as one of the early signs of constitutional syphilis, is the most frequent of these buccal syphilides. It consists in a reddening of the tonsils, the pharynx, the uvula, or the soft palate, which is sharply defined anteriorly. It gives the patient little trouble as a rule. Syphilitic laryngitis is also not infrequent. In these cases the voice acquires a peculiar roughness which may progress to complete aphonia.

Late Secondary Syphilis.—This is a form of the disease to which Fournier gave special attention.[1] It consists of secondary phenomena manifested late in the disease, and of such cases Fournier found nearly 1100 examples in a series of 19,000 syphilitic patients. The symptoms may occur at any period of the disease, even so late as in the thirty-first year. What is most interesting is that the late secondary phenomena apparently occur most often in the cases which have been well treated, in direct contradistinction to the tertiary phenomena. This does not contra-indicate efficient treatment, for it is the tertiary phenomena which are to feared. Any of the secondary symptoms may occur in this form of the disease, but the following are most often seen:

(*a*) *Cutaneous Syphilides.*—Any one of the secondary eruptions may occur, but when seen in this late stage the peculiar feature of them is their attentuated, abortive character. The recurrent roseola, for example, consists of circumscribed, regional, discrete, large, pale, and tender lesions. Quite frequent, too, is the tertiary erythema, which consists of a single, very superficial reddening of the skin, without infiltration, and free from scales.

(*b*) *Iritis*, which is essentially a secondary phenomenon, may occur in the tertiary stage and even years after the chancre.

(*c*) Most important are the *mucous syphilides*, particularly those of the mouth, which, in the secondary form, occur with extraordinary

[1] *Syphilis secondaire tardive*, A. Fournier, Paris, 1906.

frequency long after the secondary stage. *Glossite dépapillante* and many scrotal and genital syphilides are among the most common secondary mucous lesions seen in the late stage.

These are not in themselves serious but are particularly important from the standpoint of contagion. "Late secondary syphilis has for a corollary late syphilitic contagion." Therefore one should watch carefully the cases of benign recurring syphilis (with recrudescences of secondary manifestations), and particularly those complicated by nicotine stomatitis, which seems to be a determining factor in the occurrence of the glossitis so characteristic of late secondary syphilis.

The Tertiary Stage.—The secondary stage has no sharply marked terminal limit; but as it progresses the intervals of freedom from symptoms increase in extent and the symptoms themselves are diminished in severity until finally an extended period of latency supervenes. This may continue throughout the patient's life and mark the end of the disease; on the other hand, it may mean only an abatement of symptoms which, with the advent of the tertiary stage, again appear. On the average the tertiary phenomena appear about three or four years after the chancre; but they may, in precocious cases of galloping syphilis, be present at the end of a few months, and in others they succeed the secondary phenomena without any interval of freedom from symptoms. They may again appear as late as fifty-five years after the initial sclerosis, and in a fair proportion of cases they are wanting altogether. They may be preceded by any one of a group of Hutchinson's so-called "intermediate symptoms:" gumma of the testicle, psoriasis palmaris, choroiditis, arterial disease expressed in convulsions, visceral engorgement, nervous symptoms (retinitis, etc.), and rupia.

Just what determines the appearance of tertiary symptoms is not known. Certainly the absence of treatment, as Fournier so strongly insisted, is an important factor; of 2396 cases of tertiarism collected by him, 78 per cent. had not been treated at all, 19 per cent. had received moderate treatment, and only 3 per cent. had been properly treated. On the other hand, the gravity of the early syphilis bears no distinct relation to the probability of the appearance of tertiary symptoms; benign cases, and even cases without secondary symptoms, often pass through a typical or severe tertiary stage. Alcoholism and all conditions favoring lowered resistance seem to predispose to tertiary syphilis. In general the lesions of the tertiary stage are distinguished from those of the secondary by their lack of orderly appearance and progression, persistence, asymmetrical and local arrangement, relative non-infectiousness, and their tendency to ulceration.

The Visceral Affections.—These form a most important clinical group. They are not, it is true, absolutely confined to the tertiary stage, but as they are much more frequent then than at earlier stages, it is convenient to consider them together in this place.

I. **Syphilis of the Respiratory System.**—1. Trachea and Bronchi.—Tracheal and bronchial catarrh may occur in the secondary stage. Later there are more serious lesions, which while relatively rare have great importance from the fact that in almost every instance life is threatened,

and the mortality in the whole group of cases is very high. L. A. Conner has studied the subject very thoroughly.[1] In an analysis of 128 recorded cases men and women were about equally affected. In 10 cases the lesions were ascribed to congenital syphilis. The average duration of the infection was about ten years; 97 of the cases came to autopsy. The lesions were: (*a*) *Gummata*, 20 cases; the lesions were sometimes single, in others the tumor extended over a considerable area of the trachea or involved the whole circumference. (*b*) *Ulcers* were present in 44 per cent. of the cases, and, as a rule, were large and deep. In many cases the cartilages were eroded and fragments had been coughed up. Perforation of the trachea or of a bronchus occurred in 12 cases, in 5 with fatal hemorrhage. This group is very important with reference to the acute ulcerative perforation of large bloodvessels. In 2 cases an ulcer of the right bronchus perforated a branch of the pulmonary artery. In the case of Bernays, of St. Louis, a small ulcer of the trachea perforated the arch of the aorta. In Turner's case an ulcer just above the orifice of the right bronchus perforated the superior vena cava, and in Watson's case an ulcer of the left bronchus perforated a branch of the bronchial artery. In 2 instances the œsophagus was perforated. In several cases the ulcer perforated into the peritracheal tissues, with the formation of an abscess and once with tracheocele. (*c*) *Endotracheal scarring and contractions:* in 40 per cent. of the cases there were scars, bands, or obliterative endotracheitis, with marked stenosis. In some of these cases ulceration seems not to have been a preceding condition, but a slow, progressive proliferation of the submucous tissues led to gradual narrowing of the lumen. (*d*) *Fibrous peritracheitis:* of this there were 8 cases in Conner's series. The trachea and the main bronchi are encased in a dense mass of connective tissue which involved not infrequently the recurrent laryngeal nerves. It is probable that the peritracheal lesions start as gummata of the lymph glands between the trachea and the œsophagus, and finally lead to a fibrous peritracheitis.

The associated lesions are most important. Syphilis of the lungs was present in 10 cases. Dilatation of the trachea was present 3 times, in each instance above the point of stricture. It is remarkable that bronchiectasis was not more frequent, only 20 per cent., considering that in all but about 15 per cent. of the cases obstruction of some sort existed.

Symptoms.—Cough, dyspnœa (often paroxysmal), and stridor are the special features. The expectoration is often blood-stained, purulent, and fetid, sometimes containing fragments of tracheal cartilages. Profuse hemorrhage, when it occurs, is usually from a large vessel and is promptly fatal. Progressive dyspnœa, one of the most constant symptoms, is usually associated with attacks of orthopnœa and cyanosis, which may come on with great suddenness and rapidly prove fatal. This peculiar feature of paroxysmal, intermittent dyspnœa has attracted the attention of many writers. Grossmann and others regard this type of dyspnœa as an effect rather of cardiac insufficiency than of the actual stenosis. No symptom is more striking than the stridor, which is present in about

[1] *Am. Jour. Med. Sci.*, 1903, **126**, 57.

50 per cent. of the cases. It may occur with inspiration alone or with both acts. It may be of the loud, roaring character; more commonly it is of higher pitch and sometimes it is quite sibilant. Among other symptoms are pain, which is not very frequent, and tenderness over the trachea. Aphonia was present in some cases even when the larynx was normal. Retraction of tissues at the root of the neck during inspiration is not infrequent. Gerhardt called attention to the limitation of the vertical movement of the larynx in tracheal stenosis as an important differential sign from the laryngeal form.

The *diagnosis* is not often made in the cases without stenosis, unless ulcers and scars are seen in the trachea by laryngoscopical examination. With tracheal or bronchial narrowing the clinical picture is very definite: (1) A peculiar type of dyspnœic breathing in which the prolonged, labored and relatively slight inspiration and the shorter, easy expiration follow each other without the usual pauses; (2) a stridulous sound, chiefly or altogether inspiratory; (3) in most cases an inspiratory sinking in of the tissues of the root of the neck, the epigastrium, and the lower intercostal spaces (Conner.)

The *prognosis* is grave; the mortality among 128 cases was 76 per cent. In 11 of the cases death occurred in an attack of suffocative dyspnœa, in 4 it was due to hemorrhage. The *treatment* is not very satisfactory. In a few cases antisyphilitic measures have been successful. Schroetter treated some cases successfully with dilatation, done also in narrowing of a main bronchus. Tracheotomy was performed in 17 cases of Conner's list, in only 2 with permanent improvement.

2. Lung.—With the discovery of the specific organism we may expect more light on the problem of pulmonary syphilis. All are agreed that the lungs are rarely attacked, few are agreed as to the distinctive features of the lesions, and fewer still as to the clinical symptoms.

Many of the old writers in the sixteenth and seventeenth centuries spoke of a phthisis originating in lues, but it was not until the latter half of the nineteenth century that the attention of pathologists was particularly directed to the subject. Depaul in France, Virchow and Wagner in Germany, were the first to describe the lesions in the congenital and acquired forms. The literature is very fully given by Flockermann[1] and Herxheimer.[2] Anatomically the disease is rare. Among 2500 autopsies at the Johns Hopkins Hospital there were 12 cases in which lesions believed to be syphilitic were present. J. K. Fowler, who has given us the best study of the disease which has appeared in English,[3] was only able to find 12 specimens in the London museums, and 2 of these were of a doubtful nature.

Clinically the disease is rarely recognized. In not one of the cases seen by the senior writer in which the condition was suspected was it certain, and in none of these was the diagnosis confirmed postmortem. On the other hand, there are clinicians who believe that a great many cases which we regard as tuberculous have in reality a syphilitic origin.

[1] *Centralblatt f. allg. Path.*, Band **10**.
[2] Lubarsch und Ostertag: *Ergebnisse*, Jahrg. **11**, 1907.
[3] *Diseases of the Lungs*, London, 1898.

The difficulty in reaching the conclusions as to the nature of a case may be gathered from the fact that of Hiller's 84 collected cases with autopsies, Councilman regards only 28 as shown to be definitely syphilitic. It is more convenient to consider the congenital and acquired conditions separately.

Congenital Pulmonary Syphilis.—Gummata are exceedingly rare. The common lesion is the so-called *white pneumonia*. Virchow described in the lungs of stillborn children a diffuse change, sometimes involving all the lobes and causing a marked consolidation with great increase in volume. While the children, as a rule, are stillborn and premature, yet sometimes they are born at term and live for several hours. In other cases or in other parts of the same lung the surface is less uniform, and presents a more grayish tint, and is firmer, indicating that sclerotic changes have occurred. This so-called interstitial pneumonia is only an advanced stage of the other process and is due to the great increase in the alveolar and interlobular connective tissue. Sections prepared by proper methods show in these lesions an extraordinary number of spirochetes. While the majority of all cases of congenital pulmonary syphilis have only an anatomical interest, there are a few cases in which the lesions have appeared later in life; but it may be very difficult to determine the exact nature, as the coexistence of tuberculosis with syphilis in young infants is not uncommon.

Acquired Syphilis.—The lesions may be described as follows: (1) *Gummata* are rare and involve, as a rule, the neighborhood of the hilus and the lower lobes. They have the usual appearances of these structures and vary in size from a hazelnut to a hen's egg. They may soften and break into bronchi, or they may undergo sclerotic changes leading to extensive shrinkage of the lung tissue and to bronchiectasis. (2) *Bronchopneumomia.* Some pathologists regard an exudative syphilitic pneumonia as very doubtful. New investigations should now determine this point. The case recorded by Délèpine and Sisley[1] shows one way in which the lung may be involved. An enormous gumma of the right lobe of the liver, measuring $5\frac{1}{2}$ by $4\frac{1}{2}$ inches in extent, pushed up the diaphragm, to which it was firmly adherent, and extended through and involved the lower lobe of the lung. There were patches of caseous pneumonia and others looking like catarrhal pneumonia. With these there was sclerotic induration. The specimen, one of the most remarkable ever described, is figured in Rolleston's work on the liver. (3) *Sclerotic patches, chronic interstitial pneumonia.* At the root of a lung, more particularly, but scattered anywhere throughout the tissues, sometimes mapping out a large group of lobules, or radiating from the hilus of the lung, are long strands of fibrous tissue fissuring and dividing the organ, the pulmo lobatus of Virchow. In advanced cases bronchiectasis occurs or there may be cavity formation. When these scars occur alone, without gummata in the neighborhood and without signs of syphilis elsewhere, it is impossible to determine their exact nature but when such lesions coexist with gummata, or when they actually surround or extend from them, the syphilitic character is evident.

[1] *Pathological Society Transactions*, London, **42**.

The *symptoms* of pulmonary syphilis are very uncertain. Practically they are those of tuberculosis, but with the physical signs more commonly at the root of the lung and toward the base. The clinical features are often those of chronic bronchiectasis or fibroid tuberculosis. In the cases with tracheal or bronchial stenosis, dyspnœa is a special feature. Hemoptysis may occur. There may be no fever, but when softening has occurred or when there are large bronchiectatic cavities the temperature may be of the hectic type. J. K. Fowler lays down the following conditions necessary to determine the syphilitic nature of a case with progressive disease of the lung: "(1) The cases must be complete, that is, the symptoms observed during life must be considered in connection with the lesions described in postmortem examination; (2) the evidence of syphilitic infection must be undoubted; (3) repeated examination of the sputum must have been made and tubercle bacilli have been invariably absent, and the absence of tubercle from the lungs (as the cause of the lesions) must be proved by postmortem examination; (4) syphilitic lesions about the nature of which there can be no doubt must be found in other organs."

The relations of syphilis and tuberculosis are thus described by the same writer with admirable clearness. "(1) Tubercle usually affects the apex of the lung and subsequently the apex of the lower lobe and tends to progress in a certain route. The primary lesion of syphilis is often about the root and central part of the lung. The disease follows no definite line of march and gummata may be found in any position. (2) Both tuberculosis and gumma may undergo either necrosis and caseation or fibrous transformation, but with caseous tubercle the tendency toward softening and cavity formation is the rule, whereas a caseous gumma very rarely breaks down. (3) The progressive destruction of the lung by a process of disintegration leading to a gradual increase in size of a cavity, a change so commonly observed in tuberculous disease, is rarely if ever observed in syphilis, except as a secondary result of stenosis of one of the main bronchi. (4) In nearly all cases of advanced destruction of the lung occurring in the subjects of syphilis, stenosis either of the trachea or of one of the main bronchi is present, whereas this lesion is very rare indeed in tuberculosis. (5) The cavities found in cases of pulmonary syphilis are usually bronchiectatic, but not invariably so; whereas in tuberculosis they are commonly due to progressive destruction of the lung, but may be bronchiectatic. (6) The tendency to the formation of pulmonary aneurism, which is so marked a feature in tuberculosis, is rarely observed in pulmonary syphilis. (7) Pulmonary lesions in tuberculosis are very common, whereas in syphilis they are extremely rare" (Fowler.)

II. **Syphilis of the Alimentary Canal and Abdominal Organs.**—1. Salivary Glands and Pancreas.—Swelling of the *salivary glands* occurs in the secondary stage and may be well-developed before mercurials have been given. The condition may resemble mumps. Chronic bilateral parotitis with enlargement, a not very uncommon condition, is probably not connected with syphilis. Gummata of the salivary glands have been described, sometimes with ulceration.

The *pancreas* has been thought to be but rarely attacked and Herxheimer gives only 3 cases from the literature, all with gummata. Warthin in his recent studies, however, has found the pancreas very frequently the seat of histological changes which he regards as characteristic of syphilis (localized plasma-cell infiltrations, slight fibroblastic proliferation, œdematous or mucoid stroma and fibrosis). In 11 of 12 cases of diabetes coming to autopsy he detected in the pancreas (and other organs) the microscopic changes believed by him to be indicative of latent syphilis. These ideas, it must be said, have thus far received no confirmation and all the clinical evidence at hand is opposed to the view that syphilis stands in any important causal relationship to diabetes.

2. Œsophagus.—In a few rare instances ulceration of this part has been seen, usually as an extension from the pharynx. Stenosis as a sequel of the ulceration has been described by Virchow and others.

3. Stomach.—The development of roentgenological knowledge of the stomach and its diseases, as well as of the laboratory aids to the diagnosis of syphilis, has made it evident that syphilis of the stomach is much less rare than had been supposed and has invested this condition with a degree of clinical importance that was altogether lacking formerly. The subject will be discussed under Diseases of the Stomach.

4. Intestine.—In the small bowel, which is less frequently involved, there may be enteritis, gummata, ulceration with consecutive cicatrization and narrowing. The so-called syphilitic *enteritis* offers nothing peculiar. There is swelling of the lymphatic follicles, sometimes with small ulcers. In long-standing cases of tertiary syphilis with chronic diarrhœa, amyloid degeneration of the mucous membrane is not uncommon, sometimes with ulceration.

Ulcers.—Apart from the follicular ulcers, there may be extensive loss of substance due to the breaking down of gummata. The ulcers involve the lower part of the jejunum and the ileum. In a few cases perforation has taken place. Healing of the ulcers may lead to cicatricial contraction with stenosis, and there are cases on record in which in several places the calibre of the jejunum and ileum was narrowed. Appendicitis has been attributed to syphilis, but there is no evidence that persons with this disease are more frequently attacked than others.

5. Rectum. The special liability of this part to the disease is doubtless the result of a direct infection by the secretion, either from the vulva or from condylomata. In a few instances the ulceration follows the breaking down of gummata. The loss of substance, often very extensive, is usually circular, and in healing leads to marked stenosis. The condition is very much more frequent in women than in men. The stage of ulceration may be latent, and the patient is not infrequently first seen when narrowing has already taken place. The wall of the bowel is greatly thickened, the muscular coat much hypertrophied, the mucosa roughened, or actually ulcerated, and the lumen narrowed so as to admit the little finger with difficulty. Periproctitis is a common sequence, and in women the pelvic peritoneum may be greatly thickened. The ulcers may perforate with the formation of a pelvic abscess or a rectovaginal fistula. The diagnosis from carcinoma sometimes offers difficulty and the syph-

ilitic rectum has been excised for cancer. The greater frequency in women, the marked thickening of the walls with narrowing of the lumen, and the absence of definite marginal growths about the ulcers are important points. The presence of other lesions, the fact of recurring miscarriages in a woman or syphilitic lesions in the husband may help in the diagnosis. A remarkable form of syphilitic *tumor* of the pelvis has been described in which the connective tissue is chiefly involved, forming a dense mass in which the organs are embedded. Herxheimer cites 4 cases from the literature and reports 1 of his own. In one instance the pelvis was occupied by a tumor the size of two fists, situated between the bladder and the rectum, and which during life was thought to be cancer. The mucosa of the rectum may be intact.

6. Spleen.—In the early stages of the disease enlargement may usually be determined, and Moxon described an acute syphilitic splenitis.

Gummata are common, particularly when the liver is involved. The substance of the organ may be thickly set with growths varying in size from a walnut to a large orange. Wilks'[1] description and figures are excellent, and he was one of the first to recognize the true nature of these bodies. They are very rare in the congenital form (Still).

Gummatous Cicatrices.—More frequently the organ is enlarged, the capsule thickened, the surface indented and scarred and fissured, even divided into four or five sections; the liver and spleen may look very much alike. The greatly enlarged and irregular organ may present a remarkable degree of mobility.

Amyloid Spleen.—In long-standing cases, particularly those with disease of the bone and of the rectum, amyloid change is common, either as a diffuse process with enlargement of the organ or limited to the Malpighian bodies, the so-called sago spleen. In certain cases of syphilis with enlargement of the liver and spleen, leukemia may be suspected. In a case of congenital syphilis with an extraordinarily fissured liver, the spleen weighed more than 1500 gm. It was the most prominent feature in the distended abdomen. There was great increase of the leukocytes and the case was regarded as one of leukemia until the postmortem showed the existence of congenital syphilis.

7. Liver.—The literature is very fully given by Herxheimer in Lubarsch and Ostertag's *Ergebnisse*, Jahrg, xi, and the whole subject is discussed at length in Rolleston's work on *Diseases of the Liver*.

Incidence.—It is difficult to determine the frequency with which the liver is involved. Once attention has been called to the subject and the special features have been recognized the cases are found to be not uncommon; in the records at the Johns Hopkins Hospital during a period of eighteen years there were 30 cases diagnosed as such, while in the postmortem room among 2500 autopsies there were 40 cases showing gummata or syphilitic cicatrices (20 of each) and 15 additional cases regarded as syphilitic cirrhosis. In the necropsy statistics from Bellevue Hospital, Symmers, among 314 cases showing macroscopic evidences of syphilis, found involvement of the liver in one third. The incidence in

[1] *Transactions of the Pathological Society of London*, 1871.

congenital syphilis has been given at from 40 to 70 per cent. of cases of infants born prematurely or dying shortly after birth.

Morbid Anatomy.—The lesions may be described in four groups: (1) *Diffuse interstitial hepatitis.* This is common in the congenital form, in which the liver is usually enlarged, very firm, with a peculiar color, described as grayish yellow or having more the appearance of flint—the *foie silex* (Gubler). The cut surface may be uniform, and frequently miliary gummata are to be seen. The process may be much more advanced in some parts of the liver than in others, and there may be large areas of fibrosis. (2) *Gummata.* These consist of large, opaque, white tumors, usually firm and solid, the cut surface resembling a section of potato and much denser and harder than the ordinary cheesy matter of tuberculosis. Surrounding the gumma is a definite zone or capsule of connective tissue, and outside that a zone of translucent tissue representing the small-celled infiltration of the advancing syphilitic process. In fresh gummata of all sizes the three zones may be recognized. In old ones the translucent zone is absent. The tumors vary in size from small nodules of from 2 to 4 mm. in diameter to huge tumors the size of two fists. They may be solitary, more frequently there are from 3 to 4 or in some instances 12 or more. Gummata undergo retrogressive changes. Just as with the massive subcutaneous, muscular, or periosteal tumors, those of the liver may disappear completely, leaving only a fibrous scar. Softening may occur in the centre of a large gumma, either from the breaking down of the necrotic tissue or occasionally from septic infection. No change may occur in the consistency of a large gumma while it is undergoing even rapid absorption. Calcification may occur, and the rare instances of diffuse calcification in wide areas in the liver are probably of this character. (3) *The scarred and the botryoid liver.* There may be (*a*) small, puckered depressions on the surface, with perihepatitis, but with very little actual deformity of the organ. These small scars may be central as well as peripheral. There may be nothing in the liver itself to show that these are the remains of healed gummata, but specific lesions may be present elsewhere or in the other parts of the organ itself. (*b*) One or both lobes may be divided by bands of fibrous tissue, radiating irregularly from the hilus or following the portal canals. The bands may be from 5 to 10 mm. or more in diameter and the lobes may be greatly puckered and deformed. Sometimes there are gummata associated with these cicatrices. In extreme cases the whole surface of the organ is lobulated, and to this condition the term "botryoid" has been given. In a still more extreme form large sections of the liver may be completely isolated, or the organ may be made up of three or four sections united by flat bands of connective tissue. The liver substance may look natural or show slight cirrhotic changes. Occasionally it is amyloid. (*c*) Amyloid change may coexist with gummata, or it may occur independently in long-standing tertiary lesions.

Symptoms.—Congenital.—In the majority of cases the infants do not live. In children under two years the luetic appearance, together with an enlarged abdomen due to an increased size of the liver and the spleen, are the most usual manifestations. The enlargement of the liver is

uniform and may be very great, reaching below the level of the navel. Tumors are very rarely felt, but the organ is firm; very often the edge may be pressed readily with the finger, or through a thin-walled abdomen the shadow of the edge of the organ may be seen to descend with inspiration. As Gee pointed out years ago, enlargement of the spleen is almost constant in syphilitic children. Jaundice is not very common and when it occurs is early. Ascites is rare.

In general practice a much more important group of cases is the syphilitic hepatitis which occurs as a late manifestation. The attention of the senior author was called to this form by a very remarkable case in the practice of Palmer Howard, of Montreal: A boy, aged ten years, had for several months obscure abdominal trouble with enlargement of the liver, slight jaundice, ascites, and enlargement of the spleen. Finally, definite, irregular nodules were felt on the liver, whether tuberculous or malignant we were in doubt. One day his father was discovered to have a very characteristic palmar psoriasis. He confessed to having had a syphilitic infection as a young man. This gave us the diagnosis, and after months of serious illness the boy recovered promptly and was alive over thirty years after the attack. A number of other interesting cases were seen, several of which have been reported.[1]

J. G. Forbes[2] analyzed 132 cases of late congenital syphilis and in 34 per cent. the liver was involved, coming next to the bones (39 per cent.) as the seat of disease. The age incidence is worth noting—the first decade 26.5 per cent., second decade 57.5 per cent., third decade 12.3 per cent., fourth decade 3.7 per cent. The clinical features are often very characteristic. The facies, the interstitial keratitis, the rhagades, the Hutchinsonian teeth, the dwarfed stature, sometimes infantilism, or the clubbed fingers—one or other of these points may clinch the diagnosis in an obscure abdominal case with symptoms pointing to the liver. The symptoms do not differ materially from those of adult syphilis of the liver and there may be the three groups of cases: the enlarged, irregular liver, with pain due to the perihepatitis; fever, and an obscure abdominal condition the nature of which is entirely overlooked unless some clue is furnished. The second group, with tumor on the surface of the right or left lobe, presents no special features, and lastly there may be a final stage of the syphilitic hepatitis in which there is portal constriction, enlarged spleen, and ascites. In certain of those cases there may be marked leukocytosis and a picture resembling leukemia.

Clinical Features in the Adult.—The manifestations are most varied and the cases may be grouped, as Rolleston suggests, into (1) those with *features of hypertrophic cirrhosis.* A man with a history of a primary sore has pains in the region of the liver, slight jaundice, and on examination the organ is found to be enlarged, reaching to the navel or even a hand-breadth below it. It is usually tender and possibly a little irregular, but in some cases it may be quite smooth. (2) The cases resembling ordinary *atrophic cirrhosis with recurring ascites,* enlarged spleen, and all the ordinary features of hepatic dropsy. The portal obstruction may be

[1] Osler: *Lectures on Abdominal Tumors,* 1895.
[2] *St. Bartholomew's Hospital Reports,* **38**, 37.

due to direct pressure of large gummata on the main branches, or the stenosis may follow cicatrization. In the *Lectures on Abdominal Tumors* a case of this character is reported: this was a woman who had been frequently tapped before admission, and in whom the diagnosis of syphilitic hepatitis was made by the accidental examination of her shins. She recovered promptly and some years afterward died suddenly. The liver showed the old healed gummata. Undoubtedly many of the cases of "cured alcoholic cirrhosis" are of this nature. It is sometimes impossible to get positive evidence of syphilis, but in a patient who has been going from bad to worse and has had to be tapped repeatedly, if recovery occurs promptly under syphilitic treatment, it is fairly good evidence as to the nature of the disease. (3) *Hepatic Tumors.* The syphiloma on the surface of the right or left lobe may form a visible or palpable tumor, or there may be multiple nodules on the surface of the organ. Several very characteristic cases are reported in the *Lectures on Abdominal Tumors.* There may be a small, solid nodule attached to the right or to the left lobe. It is painless, and may remain unchanged for months. The nature of the case may only be determined by the development of a gumma elsewhere, or a tumor may arise in the epigastrium in a patient with slight fever, anemia, loss in weight, and the diagnosis of gastric carcinoma is made; or there may be a huge tumor the size of the two fists upon the surface of a greatly enlarged liver and the volume of the tumor may throw the practitioner off the scent. An important point in the diagnosis of these cases is the almost invariable association of enlargement of the spleen. There is nothing in the tumor itself which is of help in the differentiation from malignant disease. The syphilitic liver may be just as large and irregular as the cancerous, but there is rarely the rapidity of growth or the cachexia. (4) *Amyloid Liver.* In long-standing cases with necrosis of bones and in extensive gummatous disease the liver may be greatly enlarged with amyloid degeneration. The organ may be smooth and uniform, or there may be nodular irregularities due to gummata or other cicatrices. The spleen is usually greatly enlarged. Albuminuria is usually present with dropsy, and the general features of the cases are renal. Rolleston gives a case in which the liver weighed 8 pounds and 10 ounces. (5) *Cases Resembling Abscess.* The enlargement, the tenderness, the fever, and the slight jaundice, not unnaturally lead to the suspicion of suppuration, and if in addition to these there is a prominent tumor the suspicion becomes almost a certainty. The liver has been aspirated. Sometimes a gumma becomes secondarily infected and softens and forms an abscess. (6) Lastly, there are instances in which the great enlargement of the spleen and the diminished area of the liver suggest a primary blood disease, a *splenic anemia,* or, if the liver is reduced in size, Banti's disease. Coupland reported a case in which the large spleen was removed, but the woman died from hematemesis. The liver was found to be syphilitic.

McCrae[1] has reviewed 56 cases of hepatic syphilis and draws the following conclusions: The disease presents a varied clinical picture.

[1] *Am. Jour. Med. Sci.,* 1912, **144,** 625.

Loss of weight may be a prominent symptom, fever is common, the duration of the disease may be long, and periods of improvement are frequent. There are usually features suggestive of hepatic disease, of which general enlargement and the occurrence of nodules are the commonest. The diagnosis may be obscured by ascites and other conditions.

III. **Syphilis of the Genito-urinary Tract.**—KIDNEYS.—The most important renal complication is *acute nephritis*, a not at all uncommon event, but one to which comparatively little attention has been paid. The French writers have for long recognized its importance, and Lafleur, of Montreal, brought the subject before the Association of American Physicians in 1896. Early in the nineteenth century the presence of albumin in the urine of syphilitics was noted, but it was attributed to the use of murcurials. Rayer pointed out that it occurred as a result of the disease itself, and this view has been amply sustained. There may be simply slight and transient albuminuria, such as occurs in the initial stages of any acute infection. In other instances the symptoms of nephritis become manifest within from two to four months of the initial lesion. In the majority of the cases it occurs with the cutaneous outbreak. The nephritis of later periods is of a different character, and depends upon amyloid change. The pathological changes described by Cornil resemble very closely those of scarlatinal nephritis.

The *symptoms* are those of acute or subacute nephritis. There is rarely any fever. The onset is insidious, usually without any pain in the back, and œdema is the first symptom noticed. It may be confined to the face and legs, or it may become general. The urine is diminished in quantity, smoky, contains blood, tube casts, and much albumin. After persisting for five or six weeks the albuminuria lessens, the dropsy disappears, and the patient makes a good recovery. A few cases have been reported in which death has followed in from fourteen to twenty-one days. Chronic nephritis is an occasional sequence The nephritis may also occur in congenital syphilis. Chronic interstitial nephritis is met with in old syphilitics, and is, as a rule, the sequence of arterial changes. It is more commonly a patchy atrophy of areas of the cortex than a uniform general involvement.

Amyloid disease presents no special features.

Gummata.—The kidney is not often affected; when present the tumors are small, multiple, and rarely cause symptoms; even when a dozen or more pea-sized tumors are present there may be nothing to indicate their existence. In a few cases the kidney is the seat of enormous gummous tumors. Boldby[1] reported the case of a woman, aged forty, with swelling in the right renal region. The kidney was enlarged, hard, and easily movable, and evidently the seat of a tumor of considerable size. A new-growth was diagnosed and the organ was excised. It weighed 17 ounces and the surface was nodular on section. It cut like fibrous tissue and the surface presented an appearance exactly like that of a gummatous testis. All trace of renal tissue had disappeared. The

[1] *Pathological Society Transactions*, **48**, 128.

patient recovered, but, as Boldby remarked, it must be borne in mind that a renal tumor of considerable size may be caused by syphilis, and it is probable that antisyphilitic treatment would have obviated the necessity for operation.

Bladder.—Involvement of the bladder seems to be less rare than was formerly believed. During recent years a considerable number of instances of bladder syphilis has been reported. Almost without exception the lesion has been a gummatous infiltration, with or without ulceration.

Testicle.—Tertiary involvement of the testicle is exceedingly common and is especially important from the standpoint of clinical diagnosis. Among Symmers' autopsies upon syphilitic subjects this organ was found diseased in 39 per cent. In most cases the lesion found is a diffuse interstitial orchitis with extensive connective-tissue proliferation of the stroma which ultimately leads to fibrosis and to more or less complete atrophy of the glandular tissue. The organ is generally smooth, firm and uniformly enlarged. Pain or tenderness is rarely present. In cases of long-standing, contraction of the connective tissue and atrophy of the gland may become so marked that nothing of the testicle remains but a small dense mass hardly larger than a bean. At times the interstitial orchitis is associated with one or more gummatous nodules. The disease may affect one or both testicles.

IV. **Syphilis of the Circulatory System.**—Bloodvessels.—Upon no system does the virus of the disease fall with greater intensity in all stages than upon the bloodvessels. It is safe to say that through the arteries syphilis kills more than through any other channel. Cerebrospinal lues is largely a matter of arterial disease. The gummata often originate in or about the bloodvessels. The late arteriosclerotic changes leading to fibrosis are very often due to the toxins of the disease; but, above all, the association of aneurism with syphilis gives a place of first importance to its vascular aspects. Those acute old writers, Ambrose Paré and Morgagni, appreciated very clearly the frequency of arterial disease in syphilitic patients. In his classical chapter on aneurism there is scarcely a case in which Morgagni does not refer to the presence of syphilis. The very extensive literature is given in the papers of Benda and Chiari.[1]

Gummata of Arteries.—The larger vessels are rarely the seat of distinct gummatous tumors. Three changes occur in the smaller bloodvessels:

1. *Nodular Periarteritis.*—In this form many of the branches of the circle of Willis present nodular tumors, which may be from 3 to 5 mm. in diameter, oval in shape, firm and hard, often associated with gummatous meningitis, or with large gummata. The tumors are larger and firmer than in the nodular arteritis of tuberculosis. On section the nodular process seems to be almost entirely in the adventitia, sometimes with subintimal proliferation and with great narrowing of the lumen.

2. *Acute Gummatous Endarteritis.*—This, too, is most frequently seen in the cerebral arteries, but it has been described in the larger branches,

[1] *Verhandlung, der Deutsch. Path. Gesellschaft*, 1903, and Lubarsch und Ostertag's *Ergebnisse*, 1904 and 1906.

and it is quite possible that the acute perforating ulcer of the aorta is of this nature. The lesion consists of a localized gummatous infiltration of the subintimal tissue, with softening and erosion leading to the production of aneurism or to perforation. This may occur quite early in the disease.

3. *Obliterative Endarteritis.*—This is most common in arteries of medium or small calibre. It may be limited to one or two vessels, as to one of the coronaries in which it is not at all infrequent, or to a posterior tibial. The endarteritis leads to a gradual narrowing and a final obliteration of the lumen. There is nothing specific in the process itself. It is a lesion met with in comparatively young persons with syphilis, which may be associated with gummatous lesions. An identical endarteritis occurs as a senile change or as a result of toxic agents.

Syphilitic Arteritis.—This is seen chiefly in the large branches, particularly the aorta, and is one of the most important of all the lesions of syphilis. It has nothing to do with the ordinary atheroma. While it may occur in persons above the middle period of life, it is most commonly seen in those under forty. It presents several special features: (*a*) The process may be limited to a small section of the aorta, an inch or so, for example, at the root, or a patch extending for a couple of inches in extent anywhere in its course. The intima in the rest of the extent may be quite smooth. The parts of the aorta most frequently involved are the root, and the lower part of the thoracic and lower part of the abdominal aorta. The appearance differs very markedly from that seen in ordinary atheroma, particularly in the absence of calcification and of fatty degeneration and of areas of atheromatous softening. While in the early stage the intima may be smooth and the mesarteritis entirely microscopic, in the later stages the intima presents the appearance of what Marchand called the scarring sclerosis. The intima looks wrinkled with linear depressions or little pockets, or there may be puckerings or scar-like fissures, sometimes arranged in a radial manner. The bottom of some of these depressions has a bluish tint, and held up to the light the vessel here looks translucent. (*b*) Microscopically the changes are very remarkable and consist in (1) extensive degeneration of the elastic fibres of the media, shown very well with the Weigert stain; (2) areas of small-celled infiltration, sometimes focal, sometimes linear. These two features of destruction of the elastic and of the muscular elements, with the widespread, small-celled infiltration often localized sharply in a media otherwise healthy, are the most characteristic microscopic changes. (3) The changes in the adventitia are often even more marked than in the media and consist of areas of round-celled infiltration which may be quite extensive and look like microscopic gummata. They frequently surround the arteries and extend in linear form between the boundaries of the media and adventitia, or they may be traced in direct continuity with similar linear collections in the media. With this there is a marked obliterative endarteritis and endophlebitis of the vasa vasorum. (4) In the larger areas of small-celled infiltration giant cells are found and even patches of necrosis; and lastly, and all-important, the spirochetes are found in these lesions.

It is quite possible that other acute infections may lead to similar changes, and much discussion has taken place as to the specificity of those here described, but the evidence points strongly to the fact that syphilis is, at any rate, one of the most potent factors in the production of this form of arteritis, and the discovery of the spirochete seems to clinch the view which was so well maintained by Chiari and others.

Syphilitic Aortitis.—Syphilis produces a characteristic lesion in the aorta which is responsible for most aneurisms, about 75 per cent. of the cases of aortic insufficiency in adults, many cases of dilatation of the aorta and a certain group of cases of angina pectoris. The *Treponema pallidum* has been found in the wall of the aorta. This condition has interested many observers, one of whom[1] called attention to the following characteristics: The infection of the aorta probably takes place in the secondary stage, but symptoms often fail to appear until a number of years later. Syphilitic aortitis is probably a common cause for the presence of a positive Wassermann reaction in so-called latent syphilis. The early clinical features are a positive Wassermann reaction, precordial pain, slight dyspnœa, attacks of paroxysmal dyspnœa and angina pectoris, cardiac hypertrophy, increased pulsation of the neck vessels and signs of dilatation of the aorta. The precordial pain, paroxysmal dyspnœa and angina pectoris may be temporarily or permanently relieved by injections of arsphenamine or its modifications, but in certain instances these symptoms, especially after large doses, may be aggravated for the first forty-eight hours after injection.

The Relation of Syphilis and Aneurism.—Morgagni seemed to be fully aware of an important relation between these two diseases. F. H. Welch, in 1876, called attention to the frequency of aneurism in soldiers and thought that at least 50 per cent. of the cases were associated with syphilis. Since then in the collections of statistics the percentage has ranged from 20 to 80. The more carefully the cases are looked into, the more accurately they are studied, the larger will be found to be the percentage of cases with the history of lues. One feature which has impressed the writers on the subject is that the age incidence of aneurism and of ordinary atheroma is different. In a large proportion the patients are in the third and fourth decade. The studies of Chiari, Benda, and others show that the type of mesaortitis here described is almost constantly present in cases of aortic aneurism. The recent experimental production of aneurism by the administration of epinephrine lends support to the view. The necrosis and degeneration are produced in the media, over which there may be a perfectly smooth intima; in places this may crack, and through the narrow fissure the blood passes and gradually a small aneurismal sac is produced. This is probably the sequence of events in the majority of cases of aneurism in man. The aortic wall is weakened in its most important coat by the destruction of elastic and muscular fibres, and during a sudden exertion, or spontaneously, the intima is split, with the formation of, first, a small aneurism which gradually increases in size. Of course, this does not exclude the origin of aneurism in a small proportion of cases from ordinary atheroma.

[1] Longcope: *Archiv. Intern. Med.*, 1913, **11**, 15.

The Veins.—Recent studies have shown that the veins, to a greater extent than was formerly supposed, share with the arteries a special vulnerability to the syphilitic virus. The most important and interesting form of syphilitic phlebitis is that which occurs during the secondary or eruptive period of the disease. E. Hoffmann describes three clinical types: (1) diffuse ("strangformige") phlebitis, (2) nodular periphlebitis (nodose syphilide), (3) erythema nodosum syphiliticum. Diffuse phlebitis, the most important type, affects chiefly the subcutaneous veins of the lower extremity and may involve the whole length of a vein or only a short segment of it. Frequently the extremities are affected symmetrically. The histological changes are similar to those found in the arteries. Thrombosis is common. Most of the cases have occurred in men. The second and third types have been seen chiefly in women. The lesions appear upon the lower extremities as tender, elevated nodes of reddish or violet color and of varying size which are formed by periphlebitic inflammation about small subcutaneous veins. All of these types respond promptly to anti-syphilitic treatment.

In the tertiary stage lesions of the veins are less characteristic and less frequent, but obliterating endophlebitis and periphlebitic gummatous deposits occur and are seen especially in the deep veins of the trunk, such as the hepatic, the portal and the venæ cavæ.

Syphilis of the Heart.—The cardiac lesions of syphilis may be considered under the headings of endocarditis, fibrous myocarditis, and gummata.

Endocarditis.—Whether there is an acute endocarditis caused directly by syphilis is not yet settled. Taneff recognized a verrucose syphilitic endocarditis as a very rare form. Much more commonly it is a sclerotic form which may be either mural or valvular. The former is met with as thickened patches of the endocardium, chiefly of the ventricles, sometimes in direct connection with gummata in the myocardium. It is impossible to determine the specific character of an ordinary sclerotic valvulitis in a syphilitic subject. The cases most likely to be of this nature are those in which the valves are implicated directly in scarring of the mural endocarditis or in a patch of fibrous myocarditis. There is a very important group of cases in young syphilitic subjects who come under observation with angina pectoris, and who present signs of aortic insufficiency. The semilunar valves are involved with the root of the aorta in a specific mesarteritis and peri-arteritis. A strong evidence in favor of the luetic nature is the complete relief afforded by antisyphilitic treatment, the aortic insufficiency, of course, remaining.

Fibrous Myocarditis.—This is seen most frequently in the left ventricle and near the apex. In many cases it follows directly upon endarteritis of the descending branch of the anterior coronary artery. Unless gummata are present, or there have been well-marked signs of syphilis, it may not be possible to determine the specific character of the lesion. When extensive, it may lead to aneurism of the heart. In other instances the scarring in the myocardium is due to healing of small gummata. Widespread areas of fibrous myocarditis in syphilitic patients are most frequently the result of arterial disease.

With the recent advances in our knowledge of syphilis the belief has grown that the heart escapes involvement in that disease far less often than has been supposed, not withstanding the fact that gross anatomical changes are rare. Warthin found microscopic changes in the heart muscle, which he believed to be characteristic of syphilis, in every one of his autopsies upon syphilis subjects; the essential lesion is a more or less diffuse interstitial myocarditis characterized by infiltrations of lymphocytes and plasma cells along the bloodvessels between the muscle fibres and the gradual development of new connective tissue and fibrosis.

Gumma of the Heart.—Stockmann collected 76 cases from the literature in his monograph. The gummata may be small and multiple, or there may be a tumor as large as a walnut.

The *symptoms* of syphilis of the heart are indefinite. Sudden death is not uncommon. Of the 6 cases reported by Herringham all but 1 were brought into the hospital either dead or dying. Symptoms of dilatation are perhaps the most common. Attention has been directed particularly to two forms—the syphilitic variety of Stokes-Adams disease, in which there is either a gumma at the top of the septum, as in one of Keith's cases, or a syphilitic endoarteritis. One of the cases reported by Erlanger had bradycardia and epileptiform seizures for a year or more, and recovered completely under specific treatment. The other group is the aortic insufficiency in young subjects, which may come on with attacks of angina pectoris. They also may be greatly relieved by appropriate treatment.

Syphilis of the central nervous system will be discussed under Diseases of the Nervous System.

The Tertiary Cutaneous Syphilides.—The tertiary syphilodermata are rarer than those of the secondary stage and vary less in type. They tend to become grouped or localized.

(a) The *tuberculous syphiloderm* is one of the earliest of the tertiary manifestations. The lesions appear first as small, brownish-red nodules, which gradually reach a considerable size and then undergo central disintegration. At the same time the lesion advances at the periphery by infiltration, and since this takes place more or less irregularly the ordinary picture is that of disintegrated tubercles with advancing crescentic walls of infiltration interspersed with superficial scars. The coalescence of adjacent nodules gives rise to the serpiginous and circinate syphiloderm. The eruption is usually confined to one part of the body, the forehead, the nape of the neck, the upper part of the back, and the scrotum being the favorite sites. The differentiation from lupus vulgaris and lupus erythematosus may be difficult. On the palms and soles the tuberculous syphilide is common. The lesions are often circinate and accompanied by great thickening of the horny layer of the skin.

(b) The *gummatous syphiloderm* is the most characteristic tertiary cutaneous manifestation. It appears either in the skin or subcutaneous tissue, as a pea- to walnut-sized, rounded, painless nodule—fixed to the skin when cutaneous, movable under it when subcutaneous. The gummata occur most frequently in the lower limbs and at the points where bone is directly covered by skin. The nodules increase in size;

and, after a while, softening begins at the centre. The skin becomes reddened and finally may break, a sticky, tenacious, glairy fluid being discharged and a gummatous ulceration being formed. Gummata may, however, disappear without rupture, leaving slight traces behind them. They are usually few in number and occur late in the disease, but have been seen contemporaneous with the initial sore (Mauriac). Rhinoscleroma, carcinoma, and sarcoma have to be considered in the diagnosis of cutaneous gumma.

(*c*) The *ulcerative syphiloderm* is a later development either of the tuberculous or the gummatous eruption. The shape of the ulceration is at first that of the preceding lesion; but the marginal extension is usually irregular, and ulcerations of the most varied sizes and shapes are thus produced. The base of the ulcer is irregular and covered by secretion which dries into crusts, forming the pustulocrustaceous, the ulcerocrustaceous, or the rupial eruption. The ulcerations always result in scarring. They vary greatly in extent and number.

In the mucous membranes either the tuberculous syphiloderm or gummata may be seen. Softening and ulceration occur early, the lesion being most often seen in this stage. Its commonest site is the hard and soft palate; but it may also affect the tongue, pharynx, nose, vagina, etc. Tubercles and gummata also occur in the submucous tissue, where they form irregular, ragged ulcerations. The glossitis gummosa is a typical example.

Syphilis of the Bones.—The bones are relatively frequently affected and such bone changes are seen in both the acquired and the congenital form. They belong usually to the late manifestations of the disease. The process occurs either as a periostitis or an osteitis and may be either circumscribed or diffuse. In acquired syphilis the commonest lesion is the circumscribed periostitis, seen chiefly in subcutaneous bones (tibia, clavicle, skull, ribs, sternum), which frequently follows some slight trauma. The symptoms are pain, tenderness, tumefaction and often redness, and the end-result is usually a subperiosteal bony node. Such nodes constitute one of the important stigmata of late syphilis. In children with congenital lues the periostitis is sometimes more diffused and may affect several bones, the tibiæ being those most frequently attacked.

Diffuse *osteitis*, resulting in sclerosis and the production of dense new bone, is seen in the long bones and leads to their distortion and enlargement. Circumscribed gummatous lesions, on the other hand, occur chiefly in spongy, cancellous bone and are to be found either near the end of the long bones or in the skull, ribs, sternum or vertebræ. There is rarefaction and necrosis of the bone and, occasionally, suppuration as the result of secondary infection. In syphilitic dactylitis, seen especially in the late congenital form, there are changes in both the phalangeal bones and joints, with fusiform swelling and discoloration of the affected fingers or toes.

One of the most characteristic of the early lesions of congenital syphilis is the osteochondritis or acute epiphysitis which attacks the epiphyseal junction of the long bones and the bony-cartilaginous junction of the ribs.

Syphilis of the Eye and Ear.—The Eye.—The cornea, the iris, the choroid, the retina and the optic nerve are all vulnerable in syphilis. Inflammation of the cornea is rare in acquired lues but interstitial keratitis is a common and important symptom in the late, congenital form. It appears usually between the fifth and the sixteenth year of life. Iritis, in its different forms, has been discussed. *Choroiditis* is seen usually during the first two years of the disease, occurs in both the acquired and the congenital form and usually affects both eyes. Inflammation of the retina is sometimes associated with choroiditis and sometimes is seen independently. It may be either circumscribed or diffuse. Retinal hemorrhages are rare. Inflammation of the optic nerve may involve the whole course of the nerve or may be restricted to either its intraocular portion (papillitis) or its retrobulbar segment. The last is the most frequent form and is usually the result of syphilitic meningitis or gummatous deposit in the neighborhood of the optic chiasm.

Primary optic atrophy, paralysis of the ocular muscles and disturbances of the pupil are important symptoms of tabes and other syphilitic affections of the central nervous system.

The Ear.—Deafness resulting from damage to the internal ear is a frequent symptom of late congenital syphilis and occurs also in the early tertiary period of the acquired form. The lesion may be in the labyrinth itself but in most cases the deafness is due to involvement of the auditory nerve in a basilar meningitis.

The Quarternary Stage.—Certain pathological changes bear to the disease a relation long unrecognized, but now undeniable. Fournier, who was one of the first to call attention to these changes, regarded them as of syphilitic origin, though not of syphilitic nature; and gave to the condition the name metasyphilis or parasyphilis. Many, although not all, occur long after the initial lesion; and the syphilis in its early stages may have been quite benign and have run its course without incident. Notable features are the proneness of parasyphilis to affect the central nervous system and the gravity of its prognosis. The more syphilis is studied, the more convinced one becomes that it is not the self-limited disease it was once thought to be; and the more prone one is to consider as an etiological factor the remote luetic infection of which there is a history in so many cases of the affections which have come to be known as parasyphilitic.

Moreover, recent studies of the disease have emphasized the frequency of parasyphilitic phenomena. Blaschko, from a study of life insurance statistics, reached the astonishing conclusion that one-third of all syphilitics die later of tabes, general paralysis or aortic aneurism.

(*a*) **Tabes.**—Tabes is the type, *par excellence*, of parasyphilitic affections. It was in 1875 that Fournier first taught that tabes originated in the majority of cases from syphilis. Erb found 89 per cent. of a series of 600 cases of tabes to be syphilitic; Fournier about 90 per cent. of 750 personal cases; and Marie says, "For all practical purposes tabes is always syphilitic in origin." Certain of the cases of juvenile tabes have been shown by Strümpell and others to be the manifestation of congenital syphilis. Added to the overwhelming clinical evidence as

to the syphilitic nature of tabes are the results of serological studies; so that the question is no longer, Does a relation between syphilis and tabes exist? but, What is the exact nature of that relation? "Parasyphilis" and "postsyphilis" are no longer correct terms for tabes; the disease is a part of syphilis itself.

(*b*) **General Paresis.**—The etiological relation between syphilis and general paresis was first suggested by Esmarch and Jessen in 1857; the idea has since been staunchly supported by others. The line of argument is much the same as in tabes and it is even more convincing; so that dementia paralytica must be considered among the parasyphilitic affections. Nearly 100 per cent. give a positive Wassermann reaction; and Noguchi found the *Treponema pallidum* in the central nervous system of a number of cases of general paresis. Here again clinical facts seem to point also to a causal connection between juvenile paresis and congenital syphilis.

(*c*) **Nervous Affections.**—There is a whole host of other nervous affections which have been described as parasyphilitic, but their discussion belongs rather to neurology and they can only be mentioned here. Quite important is the syphilitic neurasthenia, more particularly the syphilophobia, which inspires the afflicted patients with a colossal dread of the disease, interprets every trivial subjective sensation as a luetic manifestation, and assures its victims that all the most horrid events of syphilis are to be their portion and their offspring's. Parasyphilitic epilepsy is also a fairly well-established clinical entity; and besides these are to be mentioned hysteria, Little's disease, and hydrocephalus, among others.

(*d*) **Tongue.**—Parasyphilis frequently affects the tongue. It may take the form of fissures in persistent mucous patches or of recurrent herpes on the borders or dorsum of the tongue. But the common and serious lesion is *buccal leukoplakia*, which often degenerates into carcinoma, and is supposed to be most frequent in patients whose mouths have been subjected to the irritation of tobacco. In this condition the epithelial layers are thickened and hornified, the intercellular spaces roomy and filled with round cells. Keratohyaline drops (stained an intense red with picrocarmine and the sure sign of hornification) are present. The onion bodies, seen in epitheliomata, are often found in buccal leukoplakia. The adventitia of the vessels is thickened, there is proliferation of the connective tissue of the corium, and round-celled infiltration. The lymph and mucous follicles are also the seat of cell proliferation.

(*e*) **The Pigmented Syphilide** (*Syphilitic Vitiligo or Leukoderma*) may be regarded as parasyphilitic because it is not peculiar to syphilis (homologous eruptions being the chloasma of pregnancy, cachectic melanoderma, etc.), and because it resists specific treatment.

(*f*) The list of parasyphilitic affections may be almost indefinitely extended if one includes all the diseases in which syphilis is often an etiological factor, but against which antiluetic treatment is useless. The importance of syphilis in the production of amyloid degeneration, of arteriosclerosis, and of aneurism has been noted; diabetes insipidus is often associated with cerebral lues, and there are other instances of suspicious association of this sort which might be mentioned.

Congenital Lues.—Effect of Syphilis on Pregnancy.—The first and most marked effect of syphilis on the fetus is the interruption of pregnancy. In 330 syphilitic gravidities studied by Kassowitz, abortion or premature delivery occurred in 40 per cent. and only 60 per cent. reached term. The nearer conception is to infection, the greater the danger of interruption of pregnancy. When many conceptions occur, however, in a syphilitic woman, the specific influence apparently "wears off;" the earliest pregnancies end in abortion, then dead children are born, then living children are prematurely delivered, then full-term syphilitic children, and finally full-term, healthy children.

In pregnant women who are syphilitic, hydramnios is also frequent. The fetus of a syphilitic woman either has macerated skin or, if born at term, presents the cutaneous lesions seen in adults. There are marked visceral lesions, particularly in the liver and spleen, which are much enlarged. The bones show the osteochondritis of Wegner, and the child has the pathognomonic "little old man" facies and the other characteristics of congenital lues to be described below. Placental changes are most marked when the disease is contracted by the mother early in pregnancy. The placenta is large, weighing sometimes one-quarter as much as the fetus. It is pale, œdematous, and either friable or firm. Microscopic examination shows placental cirrhosis with endo- and periarteritis and phlebitis of the chorionic villi. The umbilical cord also shows infiltration and vascular lesions.

The ill-effects of syphilis on the children born of syphilitic parents may manifest themselves in three ways: (1) By faulty nutrition and various dystrophies; (2) by the actual signs of syphilis in the child at birth; (3) by the signs of the disease appearing some time after birth in a child born healthy.

1. **Dystrophies Syphilitic in Origin.**—The inaptitude for life transmitted by luetic parents to offspring, even when no actual syphilitic lesion is demonstrable in the child, may show itself in the intra-uterine death of the fetus. When, however, the child reaches term, even in absence of definite signs of syphilis, the luetic dystrophies are often seen. Some of the children are born small, have no resistance to gastro-intestinal and other infections, and die early. Others survive; but they remain small, atrophic, and infantile, both in physique and intellect, have very slight resistance to infections, and are particularly subject to rickets. Faulty development and diminished resistance are prominent characteristics. Numerous malformations may be added; but, although these are often seen in the children of luetic parents and seem to be syphilitic in origin, if not syphilitic in nature, most of them may be and frequently are due entirely to other causes. These malformations usually affect the cranium. Asymmetry of the skull is often seen; large frontal bosses are not uncommon; and microcephaly and other variations of the head, both in size and shape, are observed.

Other characteristic deformities are seen in the face and mouth; for example, the flattened nose and the vaulted palate. Scoliosis and spina bifida are not infrequent. Polydactylism, syndactylism, congenital luxation of the hip, and flat-foot are some of the deformities of the limbs

seen in the children of luetic parents. The heart valves are often faulty; congenital hernia is not rare; malposition of the viscera is occasionally observed, and incomplete development of testicles, breasts, and ovaries is sometimes seen. Retardation of intellectual development may be very slight, but quite often the children are slow in their mental grasp and lack attentiveness and memory; in some cases the children are congenital idiots. Deaf-mutism, deafness, strabismus, keratitis, malformation of the iris and other ocular structures are some of the deformities affecting the organs of special sense. One of the most characteristic malformations is seen in the teeth; this deformity was studied chiefly by Jonathan Hutchinson, and the "Hutchinsonian teeth" are regarded as one of the very important stigmata. The change affects the median upper incisors of the permanent set of teeth. The teeth themselves are stunted and peg-shaped, their lateral borders being curved, and their axes usually converging from base to edge. At the free-cutting border there is a single, broad, shallow, crescentic notch, or semilunar excavation. It persists for some years; but is finally obliterated by wearing down of the teeth. These changes described by Hutchinson are quite definite, and it is improper to call any malformed syphilitic teeth, "Hutchinsonian teeth." The typical changes may, however, be absent and other malformations (not themselves peculiar, as the Hutchinsonian teeth are to syphilis) may be seen. Transverse grooves and depressions are among the commoner changes, the latter sometimes taking the form of the cupuliform atrophy of Parrot. Simple microdontism is sometimes seen. Certain characteristic changes in the six year molars have been pointed out by Wall, who described the grinding surfaces as being eroded and pitted so that they have a mulberry-like appearance.

2. **Early Congenital Syphilis.**—This is the most frequent form. The signs and symptoms are characteristic and the diagnosis is usually easy. Sometimes the disease is manifest at birth, but usually the child is born healthy and thrives until about the sixth week; occasionally the symptoms appear first about the sixth month. The typical facies described by Trousseau presents the following features: The skin is yellowish, the expression wretched, the eyelashes are wanting, the hair of the head scanty, and patches of alopecia are present; later, the appearance becomes the well-known one of a "little old man." The facies of Trousseau may be absent. The appearance of actual symptoms may be preceded by a period of restlessness and wakefulness. One of the first symptoms observed is the characteristic rhinitis known as "the snuffles;" this is a coryza with serous discharge, the formation of crusts, and resulting in respiratory obstruction. The child usually at this time begins to nurse badly and nutritional disturbance supervenes. Ulceration and necrosis of the nose, with the formation of the saddle-shaped deformity, may occur. Fissures or rhagades appear at the corners or the free borders of the lips, increasing the wretched appearance of the child and greatly adding to the danger of contagion on the part of the nurse. Anemia is present. The child goes from bad to worse; it suffers from malnutrition and often succumbs to cachexia. Many of the children are carried off by intervening acute infections, particularly bronchopneumonia and

enteritis. Among good hygienic surroundings the prognosis is fair; otherwise it is grave, and in foundling hospitals practically all the children die. The glands are usually not enlarged; but a whole host of cutaneous lesions, including most of these seen in syphilis of adults and certain others peculiar to the congenital form, appear. Their severity is a clinical characteristic.

The roseola is usually wanting; but a yellowish-red, maculopapular erythema, beginning on the buttocks and thighs and extending to trunk and face, is sometimes seen.

The psoriaform syphilide is very characteristic. It consists of bright-red or copper-colored, infiltrated areas on the palms of the hand and soles of the feet, covered by white, dry scales, which are easily detached, leaving a collarette at the periphery. It corresponds to the psoriasis palmaris and plantaris syphilitica of adults.

The erythema, when situated about the body orifices, is usually accompanied by *rhagades*. These are true ulcerations, which may leave indelible scars, particularly characteristic about the lips and chin.

Mucous patches occur in the mouth and about the lips; but they show a predilection for the intergluteal groove, the perineal, genital, and genitocrural regions. This may be due in part to irritation by urine and feces in these sites. There is, however, very little tendency to condylomatous overgrowth, as in adults. Patches are also seen back of the ears and near the nose, where they are often covered by crusts.

Pemphigus neonatorum is the most characteristic of the cutaneous lesions. This syphilide is most often situated on the palms of the hands and soles of the feet. It may be present at birth, or, if appearing later, it begins as a bluish-red infiltration; the epidermis is soon raised and vesicles and bullæ are formed. Sometimes, however, there is no liquid present. The lesions are 2 mm. to 1 cm. in diameter. The epidermis is white, as if macerated, and lies in folds; below, the skin is reddish, wine-colored. The serous exudate soon becomes purulent; the vesicles become tense and are either absorbed or burst, leading to purulent ulcers, which are often serious. In malignant cases there is extensive destruction of the skin, with gangrene, necrosis, and, not infrequently, death.

Hemorrhagic Exanthemata.—Syphilis is a cause of hemorrhage in the newborn and not infrequently this occurs subcutaneously (syphilis hemorrhagica neonatorum). The hemorrhages may be subcutaneous or submucosal; sometimes they occur about the umbilicus. Of 3364 children studied by Wilson at the Philadelphia Lying-in Charity, 10 died of hemorrhage attributed to syphilis. Reduced coagulability of the blood and increased arterial tension in the newborn are the causes assigned by him. Jaundice is practically always present in some degree.

Acne syphilitica, impetigo syphilitica, and *ecthyma syphilitica* are more or less characteristic of the congenital form. The *poorly nourished skin* of children with congenital lues is also subject to many skin affections not themselves specific. Eczema intertrigo is quite common; and suppuration and destruction of the nails are not infrequent.

Bony changes are frequent and characteristic. The dystrophies of the cranium, particularly the frontal protuberances, have been mentioned.

In the limbs they often manifest themselves in the syndrome of Parrot (syphilitic pseudoparalysis of the newborn). This is characterized by immobility, pain, bony swelling, and sometimes crepitation at the epiphyseal line. There is no true paralysis, the muscles reacting to faradism and galvanism. It usually affects only one limb, but sometimes two. It may be the first sign of congenital lues; but more often appears in the third or fourth month.

Osteochondritis syphilitica, first described by Wegner, is highly characteristic of congenital lues. Its site is the boundary between diaphysis and epiphysis of the long bones (upper end of the tibia and both ends of the femur particularly) and between bone and cartilage in the ribs. Three stages are recognized. In the first there is marked proliferation of cartilage cells at the boundary of the diaphysis, forming a zone recognizable macroscopically between diaphysis and epiphysis. Within this zone ossification is irregular and retarded. In the second stage proliferation of cartilage cells advances and there is further irregular ossification at the epiphysis. In the third stage one finds bulgings of the cartilage, with thickening of perichondrium and periosteum. The cartilage forms a broad, irregularly limited zone; the portions next the spongiosa consist of a pus-like, semifluid mass. Epiphyseal separation may occur.

Visceral lesions are observed in practically all the organs of congenitally syphilitic children. Many of them are without characteristic symptoms; diarrhœa and vomiting occur, but they are not pathognomonic. Involvement of the testicle is, however, particularly characteristic; and orchitis with exudative vaginitis in an infant is always suggestive of lues. It usually ends in sclerotic atrophy. The enlargement of liver and spleen are also of clinical importance from the aid they give to diagnosis. The former is regular, smooth, and very large, reaching sometimes to the iliac fossa. It is cirrhotic, but the cirrhosis is usually unaccompanied by circulatory changes or icterus. The large, palpable spleen is also of a diagnostic import. Affections of the eye are seen in the early form of congenital syphilis, but interstitial keratitis is much less frequent than in the late form.

3. **Late Congenital Syphilis.**—This form, especially studied by Hutchinson and others, has been clinically well recognized only in comparatively recent years. Its manifestations were formerly regarded as those of acquired syphilis or dismissed as "scrofulous." It appears usually about the time of the second dentition or at puberty, and is most frequent in those who have shown signs of the early form in infancy. It occurs also, however, in patients whose childhood has been free from disease. Its manifestations are not often seen after the twenty-eighth year; but a terminal time limit is difficult to set. Any organ may show syphilitic manifestations of a gummatous, sclerous, or sclerogummatous type; but the following are those most often affected: the eyes, the bones, the skin, the throat, the pharynx, the brain, and the ear. One of the most important changes is the almost pathognomonic *interstitial keratitis*. This usually occurs between the eighth and fifteenth year, and begins as a diffuse haziness near the centre of the cornea of one eye. It is accompanied by some irritability of the eye and by dimness of vision. When

looked at more closely the corneal haziness is seen to consist of discrete, punctate deposits within the cornea itself and not on its surfaces. In a few weeks the whole cornea becomes involved, takes on the appearance of ground-glass, and is surrounded by a zone of ciliary injection. Photophobia appears and involvement of the opposite cornea takes place. The vision is quite dimmed; but soon the condition begins to improve and the cornea clears slowly. If treated early, the prognosis is fair and is inversely proportional to the degree of photophobia, but recovery is always slow and, at best, imperfect.

The cutaneous and mucous lesions of late congenital syphilis in general resemble those of acquired lues. Fissures and rhagades occur about the mouth. Changes in the bones are a marked feature; bosses are seen on the skull, and hyperostoses on the long bones. The sabre-shaped tibia is particularly characteristic; here the bone is much bowed and is increased in volume by a chronic osteoperiostitis accompanied by gummata. The latter often break down and ulcerate. Arthropathies are occasionally seen, particularly a form of synovitis which resembles white swelling and a special form of symmetrical synovitis of the knee has been described by Clutton. In the diagnosis of both the early and the late form of congenital syphilis the roentgen-rays may furnish valuable aid by revealing the skeletal changes which are rarely lacking and which are usually quite characteristic.

In typical cases the whole clinical picture is characteristic. The patients are small and poorly developed; the skin is of an earthy paleness; the forehead is prominent, the frontal eminences marked, and the skull asymmetrical; the bridge of the nose is depressed and its tip *retroussé;* there are cicatricial stigmata of the skin and mucosæ, and striæ about the mouth; there is the presence of the Hutchinsonian triad (pathognomonic alterations of the teeth, interstitial keratitis, and disturbances of hearing), there are signs of infantilism (slender physique, undeveloped testicles, rudimentary beard, and pubic hair); there is glandular enlargement often mistaken for tuberculosis; and finally there is arrested intellectual development. Further confirmation of the diagnosis may be obtained by inquiry into the family history, which will often show a high mortality or a high percentage of abortions; and, by confrontation, revealing the source of the disease in one parent or both.

Diagnosis.—**Clinical Diagnosis.**—Important as are the modern laboratory aids to the diagnosis of syphilis these should not be permitted to supplant the careful study of the patient himself; for such laboratory aids are by no means infallible and the clinical signs of syphilis are still, and probably will always remain, of equal or greater importance in its diagnosis.

The diagnostic features of the *chancre* have been discussed. In it *secondary stage* syphilis can usually be recognized without difficulty because of the fact that some at least of the many characteristic symptoms are almost certain to be present. These symptoms include the skin eruptions, the lesions of the mouth and throat, the general lymphadenopathy, the severe and persistent headache, the joint and bone pains, iritis, periostitis, loss of hair, etc.

In the *tertiary* stage, however, the clinical diagnosis often presents great difficulties because of the fact that in almost every case the periods during which the disease is quiescent greatly exceed in length those during which active manifestations exist, nevertheless the list of important and permanent stigmata is a long one and failure to recognize the disease clinically is frequently due rather to the failure to make a thorough and systematic physical examination than to the absence of all signs of the disease. The entire body should be searched for characteristic skin eruptions and suspicious scars; the eye for signs of an old iritis and for abnormalities of the pupil. Precocious and marked deafness should be carefully investigated. Examination of the mouth and throat may reveal mucous patches, ulcers, scars, perforation or deformity of the palate; the tongue may show gummatous nodular ulcers, old fissures, leukoplakia or the indurated smooth atrophy of the base (behind the circumvallate papillæ) which is present in such a surprisingly large proportion of cases of late syphilis. Palpation of the superficial lymph nodes may reveal a more or less general enlargement. Periosteal nodes may be found on such bones as the tibiæ, clavicles, ribs or skull. Examination of the heart and aorta may yield important signs in the form of dilatation of the aorta, aortic insufficiency or aneurism. A much enlarged or irregular liver or spleen is always to be regarded with suspicion and changes in the contours and consistence of one or both testicles may indicate the existence of syphilitic orchitis, one of the commonest of the late lesions. Finally, evidence of syphilis of the central nervous system may be disclosed by abnormalities in the deep reflexes, the gait, the skin sensibility and the pupils.

Laboratory Aids to Diagnosis.*—Our ability to recognize syphilis has been enormously increased by the development of the various laboratory methods devised for that purpose. These include the actual demonstration of the *Treponema pallidum* by dark-field illumination and special staining methods for tissues, the Wassermann complement-fixation test and its modifications, the luetin test, the various forms of examination of the cerebrospinal liquid, and the roentgen-ray examination.

The demonstration of the spirochete by the *dark-field-illumination method* has its special field of usefulness in the primary and early secondary stages when the organisms are, as a rule, easily found in the chancre and skin eruptions. Especially valuable is its use in the prompt identification of the chancre, for at that time the Wassermann test frequently fails to give a positive reaction; yet this is the time when a correct diagnosis is of paramount importance, not only in order to prevent the spread of the infection but because at this time intensive abortive treatment offers the best chance of success.

The Wassermann Reaction.—It was the fundamental discovery made by Bordet and Gengou of the principle of complement deviation which led Wassermann to study the blood-serum of syphilitic patients and to devise the important biological test which bears his name. The reaction depends on the capacity possessed by the blood-serum of syphilitic

* For a full discussion of this subject consult Browning and Mackenzie, *Recent Methods in the Diagnosis and Treatment of Syphilis*, London, 1924, 2d ed.

patients to fix complement in the presence of extracts of syphilitic tissue, or certain other alcoholic extracts. This fixation of complement is tested for by the use of a so-called hemolytic system, which consists of red blood cells and a serum capable—in the presence of complement—of hemolyzing them.

It is now well recognized that the complement-fixation test as applied to syphilis is not specific in the sense of being a true antigen-antibody reaction; nevertheless the value of the Wassermann test has been proved beyond all question and for practical purposes a positive response may be regarded as almost certain evidence of the existence of syphilis if the technique is properly carried out and if certain exceptional causes of a positive reaction be excluded. Craig, among 4000 tests made upon non-syphilitic patients, obtained a positive test only 12 times. Five of these patients were in the active stage of tertian malarial fever. A positive reaction may also occasionally be obtained in yaws, leprosy, relapsing fever and diabetes. Rarely also a positive test may be produced by the sera of patients in the midst of an acute infection such as pneumonia and scarlet fever. The Wassermann reaction usually does not become positive until sometime after the appearance of the chancre. Craig's statistics, from studies made in the U. S. Army, show a positive reaction in the first week after the appearance of the chancre in 36 per cent. of the cases tested, 59 per cent. in the second week, 69 per cent. in the third, 77 per cent. in the fourth, and in the fifth week 81 per cent. During the secondary stage of the disease the reaction was positive in 96 per cent., during the tertiary stage 87 per cent., and in latent syphilis a positive response was obtained in 68 per cent. A *negative* response to the Wassermann test furnishes much less decisive evidence of the absence of syphilis than does a positive response of its existence. Particularly in the late period of the disease both acquired and congenital, is a negative reaction not infrequently obtained. This is especially true of those cases in which the lesions are limited to the central nervous system or to the circulatory system. A single negative reaction, therefore, cannot be said certainly to exclude a syphilitic infection even in the absence of all symptoms and of a history of the disease. If however, the test fails to give a positive reaction in any of several examinations made over a period of some months the probability that no syphilis exists becomes almost a certainty.

Since the introduction of the Wassermann test many modifications of its technique have been proposed, in the effort to render it more sensitive or to simplify its procedure. It was very soon found that an antigen made of an alcoholic extract of certain animal tissues, especially heart muscle, was more satisfactory than that made from syphilitic tissues, and at present the antigen in common use is an alcoholic extract of beef heart. By the addition of a small amount of cholesterin to such an alcoholic extract the sensitiveness of the reaction can be considerably augmented, and the percentage of positive reactions in syphilis thereby increased. Unfortunately, however, such a cholesterinized antigen also increases the likelihood of a positive response in conditions other than syphilis. The modification of the Wassermann technique devised by Kolmer seems to be both sensitive and accurate and is gaining in popularity. Its only

disadvantage is that its technique is somewhat complicated and time-consuming. The modifications known as "Precipitation tests," of which those of Kahn, Meinecke, Sachs-Georgi, and Dreyer are examples, all possess the virtue of a much simplified technique but have not yet come into general use.

The Provocative Wassermann Test.—This procedure was suggested by Gemmerlich as a means of eliciting a positive reaction in suspicious cases, or in those presumed to be cured of the disease, in which the Wassermann test is negative. It consists in the intravenous administration of a small dose (0.3 or 0.4 gm.) of arsphenamine and the testing of the blood each day during the succeeding week. While the value of this method has often been questioned there seems to be no doubt that by it the sensitiveness of the Wassermann test can be somewhat increased. The application to the spinal fluid of the test has proved of great value in the diagnosis of syphilitic affections of the central nervous system and a positive reaction may often be obtained in this fluid when the blood reaction is quite negative. The sensitiveness of the test varies considerably with the quantity of spinal fluid employed. When a large amount (1 cc.) is used the reaction is positive in practically all cases of general paresis and cerebrospinal syphilis and in about 90 per cent. of the cases of tabes.

The Luetin Test.—This procedure, introduced by Noguchi[1] in 1911, has been proved to be distinctly less reliable than the Wassermann reaction and has not come into general use. It consists of the intradermal injection of a dead culture of the *Treponema pallidum* and depends upon the production of a local skin reaction as the result of an allergic response from the tissues comparable to the cutaneous tuberculin reaction. A positive reaction was obtained by Noguchi in rather less than 30 per cent. of the cases of primary syphilis, in 47 per cent. of cases in the secondary stage, and in 80 per cent. of the tertiary cases. The best results were obtained in cases of luetic aortitis and aortic insufficiency. The reaction was positive in about 70 per cent. of those afflicted with congenital syphilis and in about 60 per cent. of patients with tabes and general paresis. Sherrick has shown, however, that a positive reaction to the test frequently may be obtained in non-syphilitic persons who have been receiving potassium iodide or other iodine-containing drugs even though the iodine may have been discontinued some days before the test.

Prognosis.—Although it is still possible to say that syphilis is a curable disease it seems quite certain, in the light of modern knowledge, that a complete cure is of much rarer occurrence than was formerly believed. Unfortunately, the only convincing evidence of a complete cure of syphilis is still the event of a reinfection. That the recorded number of such reinfections should be steadily increasing is, in itself, one indication of the effectiveness of the present-day methods of treatment. The clinical records of large numbers of cases carefully studied over long periods of years justifies the following conclusions as to the outlook for a luetic patient:

1. In general, the prognosis for the average case is good with careful

[1] *Jour. Exper. Med.*, 1911, **14**, 196.

treatment and bad without it. This holds for the secondary phenomena, for tertiarism, and for the transmission to progeny.

2. No deduction as to the virulence of the disease is to be drawn from the character of the chancre; phagedenic sores may introduce a mild syphilis and herpetic chancres a malignant one. Nor do the secondary symptoms *per se* give us any indication of the future.

3. The chances of cure are greatest for patients receiving intensive treatment at the earliest possible moment after the appearance of the initial lesion. In general the prognosis improves *in direct proportion* with the promptness with which treatment is instituted and seems to depend largely upon the vigor and intensity of such treatment. The secondary period, if the sore has been positively diagnosed and treatment promptly begun, is as a rule only manifested by a few benign symptoms; on the other hand, cases first treated in the tertiary stage are difficult and often impossible to cure.

4. The frequency of tertiary symptoms, other things being equal, is inversely proportional to the adequacy of treatment received. The frequency of tertiary and parasyphilitic phenomena should now become less, since "latent" syphilis can be detected by the Wassermann reaction and the late features forestalled by treatment.

5. A patient who has received thorough treatment is entitled to consider his disease cured and himself a safe husband and father. We cannot, however, *guarantee* that no syphilitic phenomenon will manifest itself. We can only say that such an occurrence is extremely improbable. "Neither the dose," said Ricord, "nor the pharmaceutical preparation, not the duration of treatment, confer immunity with certainty or guarantee the complete and radical extinction of syphilis." For this reason a patient who has had syphilis should never be dismissed from observation; and he should be advised of the importance, in case of future disturbance of health, of informing his physician of his syphilitic infection.

6. Three types of syphilis may be recognized, according to course and prognosis. *Benign syphilis*, which is even occasionally seen in untreated cases, occurs most commonly in women. Here the initial lesion, a mild sore throat, a moderate roseola, and an adenopathy, perhaps with headache, make up the entire symptom-complex. *Normal syphilis* shows well-marked but not severe symptoms throughout, and the manifestations are quite amenable to treatment. After a certain time, during which a number of relapses and exacerbations occur, the disease ends, although parasyphilitic phenomena may later appear. *Malignant* or *galloping syphilis*, less frequent now than formerly, presents either the normal manifestations in severe, frequently recurring, and obstinate form, or else violent, often rapidly fatal tertiary manifestations early in the disease. The skin eruptions are ulcerative and pustular; cachexia is marked; gummatous lesions are extensive and occur early, and the internal organs are rapidly involved.

7. *Congenital syphilis* offers in general a very bad prognosis. The average mortality is probably about 75 per cent. Kassowitz states that one-third of all syphilitic infants die *in utero*, and of the remainder 34 per cent. succumb during the first six months of life. Here, again,

treatment affects the prognosis wonderfully; according to Etienne 95.5 per cent. of living syphilitic children die if untreated and only 10 per cent. if properly cared for.

8. No unanimity of opinion exists concerning the proportion of syphilitic patients that ultimately die of the disease. The percentage is variously estimated as from 15 to 70. In the insurance statistics published by Brockbank the mortality among syphilitics is shown to be 33 per cent. higher than the average for persons of corresponding age.

Syphilis and Marriage.—It is difficult to formulate a general rule which may safely be applied to every syphilitic patient contemplating marriage, for the problem is always to some extent an individual one. Certain minimal requirements, however, should be insisted upon before approval is given. The patient should have had at least several courses of treatment by arsphenamine and mercury covering a period of at least two years. He should moreover, have been free from all symptoms and have shown a negative Wassermann reaction in both blood and spinal fluid for one year after treatment has ceased. An exception to this rule probably can safely be made in certain of the so-called Wassermann-fast cases, which in spite of repeated, thorough courses of treatment and the absence of every sign of the disease still yield a positive reaction. All such patients should, however, be looked upon with suspicion and great caution exercised in assuring them that they are no longer capable of transmitting their infection.

Prophylaxis.—There are many striking things about syphilis, but none is more striking than its persistence in spite of knowledge complete enough to stamp it out. It is a disease almost unparalleled in the extent and intensity of its ravages; it is the subject of popular dread; yet it is both preventable and, within limits, curable. The close connection of the problem of syphilis with the problem of prostitution—and particularly with that of clandestine prostitution—makes it essential for the physician to familiarize himself with the hygienic significance of this industry and with the methods that have been adopted to keep it within bounds. Prostitution is the source of the disease; it is prostitution that keeps it in circulation; and no problem of greater importance to the commonwealth could be presented to the State. It cannot be said that the efforts of the State to comprehend or solve the problem have met with brilliant success. Rigid State control, with medical inspection, simple State regulation, and segregation are among the methods that have been tried. Opinions about them are varied.

The question of State regulation of prostitution, it must, however, be insisted, is really one of the minor problems connected with the problem of the prophylaxis of syphilis. Governmental supervision deals, even under the most ideal conditions, with an almost negligible fraction of the total prostitution, and leaves untouched the clandestine prostitution which is spreading disease. It is, furthermore, absurd to ask much of it, when it is remembered that law is only effectual as an expression of the predominating opinion of the commonwealth; and to expect, as has been expected, that State regulation subdue prostitution in countries where the mistress is not simply a tolerated but a well-recognized and accepted

personage, where promiscuous intercourse thrives, where the marital tie is regarded in the loosest way, is like sowing weeds and then asking for a law that no weeds shall grow.

We have then to consider those aspects of the public hygiene of syphilis not directly concerned with the attitude of the State toward prostitution.

Public Prophylaxis Concerned with Syphilis Itself.—(*a*) It has been suggested that the disease be made a reportable one and that treatment be obligatory. Aside from the very large problems which this procedure would create as to a physician's right to reveal a professional secret of this nature, it seems quite certain that a regulation of this kind would rather hinder than promote proper treatment. Enforced publicity would certainly lead to the concealment of syphilis, and many cases now well treated would go untreated.

(*b*) The establishment and maintenance of proper institutions for the study and treatment of venereal diseases is a crying need everywhere; and the commonwealth can do nothing better for the common weal in the matter of syphilis than by making this necessary provision. This is a part of the fight against the disease which has been woefully neglected; it is a part which should receive the support of every well-informed physician, as offering a well-grounded hope of accomplishing much in the attempt to eliminate the sources of infection and to diminish the miseries of the already contracted disease. The cure for syphilis is known, if it is not applied, the fault lies with the community which chooses to make no use of its knowledge; and of this blame the medical profession must accept a large share.

(*c*) *Antisyphilitic Vaccination.*—This subject has been discussed under Immunity. Unfortunately we have at the present time no vaccine or serum that has been shown to possess either prophylactic or curative power even in experimental animals, and the problem of prophylactic vaccination would seem to require much further experimentation and study before its solution is accomplished.

(*d*) A prophylactic measure of great practical importance is the effort to shorten the contagious period of syphilis by vigorous treatment of each case at the earliest possible moment that the diagnosis can be made. To accomplish this it is essential that arsphenamine be made available for every case and especially necessary that physicians generally shall be better trained in the prompt diagnosis of venereal sores and that they recognize how indispensable is the dark-field illumination in such diagnosis.

Public Prophylactic Efforts Concerned with Society and its Institutions.—Procedures of every sort have been suggested according to which the prophylaxis of syphilis was to be strengthened by some change in the legal attitude of the State toward the disease or by an alteration in the institutions of Society.

(*a*) Penalty for the transmission of syphilis has been proposed by some as a necessary and important step in the attempt to destroy it.

(*b*) Should the transmission of syphilis from husband to wife or from wife to husband constitute ground for divorce? This is a difficult question which belongs rather to law than to medicine; yet it cannot be

disregarded in considering the prophylaxis of syphilis. The hideous injustice to which a husband or a wife submits when he or she is knowingly and voluntarily infected by the other party, tempts one to provide legal redress for the predicament. Yet the procedure is a dangerous one; its application would present great practical difficulties, and it is doubtful if it would often be taken advantage of by the injured party.

(*c*) It has been urged that a certificate of health as regards venereal disease be required before marriage permits are issued, and in some communities steps have been taken in this direction. Upon one point there can be no doubt. It is the bounden duty of every physician to use every means in his power to prevent marriage between people with venereal infections. He should absolutely forbid his syphilitic patients to think of this step until they have undergone proper treatment, and he should enforce this command with complete information as to the misery sure to result from such a marriage.

(*d*) Sanitary examination of men. (1) Such an examination, together with obligatory treatment, already obtains among certain government employees, as, for instance, in some armies and navies. Diday maintained that it should apply to all government servants. It has also been suggested that all public wards (tramps, beggars, and prisoners) should be submitted to examination for syphilis. (2) The examination of customers on their entrance to brothels has been seriously urged by certain writers as a promising procedure in preventing syphilis. The idea is no new one. As early as 1430 there was a regulation requiring such an examination in London, and Diday was a strong supporter of the idea. It was tried for a while in Hamburg. The scheme is, of course, quite out of the question, for it would be perfectly impossible to find reputable physicians who would give their time to such business, and in the hands of any but such physicians it would lead to all sorts of graft and abuse. Furthermore it would simply result in an increase of free prostitution.

(*e*) It is notorious that venereal diseases furnish a large percentage of the material of charlatanism. In the case of syphilis the insufficient and unintelligent, if not actually dangerous, treatment which results is a definite menace to public health, and war on charlatanism is a distinct part of the prophylaxis of syphilis. Nowhere can neglect or ignorance bring greater misery, most often to the innocent, than in this disease; that its care should be in competent medical hands is essential to the public health. Provision for its treatment in adequate dispensaries is one phase of prophylaxis; but legal provision against the industry of quacks, a provision to which the public, with strange neglect of its welfare, is indifferent or even hostile, is equally important.

(*f*) There are certain industries (glass-blowing is one) notoriously dangerous in the transmission of syphilis; and it seems to be well within the power and duty of the State to ensure proper hygienic supervision. That vaccination should be under rigid oversight in this respect goes without saying: and the possibility of infection by surgical or dental instruments is one that has but to be mentioned in these days of careful technique. One should insist on the great care necessary in dispensaries where chancres are being constantly handled and circumcisions frequently

done, for this operation has been responsible for the transmission of the disease.

(*g*) Education offers the greatest hope. Here is a disease bringing untold misery to a large proportion of the community, rendering great numbers of citizens inefficient, and transmitting its calamities to wholly innocent parties. It is a disease the phenomena and far-reaching miseries of which are known with certainty; it is a disease which can be perfectly well avoided; it is a disease which, when contracted, can be greatly limited both in its early manifestations and its late effects. Yet it is a disease about which even the educated classes are often uninformed or woefully misinformed; while the masses depend for their information on unintelligent alarmist quacks.

1. *Education of the Medical Profession.*—Students are rarely well instructed in syphilis; they are almost never thoroughly instructed. "This explains," writes Fournier, "why medical men mistake chancres and mucous patches for something else; why they give syphilitic infants to the care of a healthy nurse, or inversely; why they regard syphilis as cured after a few months or even weeks of treatment, and why they permit marriage to uncured syphilitics." In no way, indeed, does the public health suffer more when medical errors are made than it suffers if the errors be made in regard to syphilis; and these are errors which might be avoided by adequate attention to the subject in medical curricula.

2. *Education of the Laity.*—This procedure is a delicate and difficult one. Certain suggestions may, however, be made as to possibly valuable educational undertakings.

(*a*) The first need is that the dangers of syphilis, about which the laity has the vaguest ideas, become matters of public knowledge. It is idle to expect that such knowledge would entirely protect the public; for some would continue to contract and spread the disease. There are, on the other hand, certain people who are absolutely protected from danger by a thorough knowledge of it; and it is the duty of the medical profession to see that such persons, however small a part of the community they form, do not have to purchase their knowledge at the price of experience. Just how this knowledge is to be spread is a matter for consideration on account of the unique delicacy of the task. No doubt one of the functions of a venereological dispensary is that of instruction; and it would be useful to have printed guides distributed from these centres in somewhat the same way as is done for tuberculosis.

(*b*) It is also in the interest of public health that the community should understand the dangers of prostitution. Instruction in this matter, by reason of its difficulty and delicacy, offers hope of doing good only when given with the utmost wisdom. Yet the opinions of students of the question and the success of efforts already made encourage us to hope that something may be accomplished by this form of education.

(*c*) It is incumbent on the medical profession to keep informed and to instruct the public as to the danger of innocent syphilitic contagion. Nothing can be more tragic than the disease acquired in this way, and in a large number of instances information and reasonable care would

have prevented it. The danger of transmission by wet-nurses and by many of the contacts of every-day life should be known to all men.

(*d*) The close association between alcoholic abuse and the contraction of venereal disease should be more widely appreciated.

(*e*) Lastly must be mentioned the close association between the prophylaxis of syphilis and many social reforms. Prostitution, the great source of the disease, is a part of the social fabric; and it exists, partly at least, because of the injustices of society. No movement therefore which makes for improved industrial and hygienic conditions can fail to be of service in the fight against syphilis.

The Private Hygiene of Syphilis.—There can be little doubt that the physician has a distinct duty to fulfil to his patients in explaining to them certain hygienic details which cannot well be publicly considered, and which do not enter into the prophylactic campaign of the State. There is first the question of continence, and here the physician dare teach his patients but one thing, namely, that continence, no matter how difficult, is the relation of greatest safety for the individual and for society and is not detrimental to health.

The experimental work of Roux and Metchnikoff has shown that mercurial inunctions at the site of inoculation with the syphilitic virus are effective in preventing the disease if applied within eighteen and one-half hours of the time of infection, though if applied later they are without avail. Neisser's observations seem to indicate that bringing the body immediately under a general mercurialization has no prophylactic value. In the United States Navy rigid prophylactic measures (inunctions) seem to have been, on the whole, satisfactory.

The Prophylaxis of Congenital Syphilis.—This is the most tragic form of the disease, and it is therefore unusually gratifying to know that much can be done in preventing it. The most certain prophylaxis consists in proper treatment of the parents before marriage. In statistics compiled by Fournier, it has been shown that the infantile mortality of the issue of subjects whose syphilis has been properly treated is only about 3 per cent. In 45 pregnancies, however, occurring after the marriage of untreated syphilitics, the mortality was 82 per cent.

We are here concerned rather with the question as to whether there is any hope of protecting the fetus by treating the mother. It has been shown that mercury and potassium iodide pass from mother to child through the placenta, and there is evidence that arsphenamine is similarly effective. This treatment is rational and has produced excellent results. Women, for instance, whose previous pregnancies had been disastrous, have frequently had normal pregnancies when specific treatment was instituted. Treatment to be effective must be begun in time. "After the fifth month it is too late," says Pinard. The treatment should be continued during the whole pregnancy. Pinard advises continuous treatment, but others prefer the intermittent method—twenty days' treatment and ten days' rest every month.

Treatment.—**Initial Stage.**—It is usually the appearance of the chancre which brings syphilitic patients for treatment. In many instances, it is true, the chancre is entirely overlooked or neglected and the patients

are first seen with secondary or tertiary symptoms; but as a rule the physician's therapeutic problems begin with the chancre itself. The idea that syphilis might be extinguished *ab ovo*, by treatment directed at its initial lesion, has always been attractive; and blockading, excision, and cauterization of the chancre have been practised. By general consent however, the practice has gradually been abandoned. Recent experimental work has made it evident that by the time the chancre has appeared the infecting organisms have not only reached the regional lymph nodes but have invaded the circulating blood.

The treatment of the chancre consists, as a rule, in doing nothing. This is particularly important if there is any doubt about the diagnosis; for cauterization of the sore will destroy its normal appearance, prevent its normal evolution, and thus make the diagnosis further impossible before appearance of constitutional symptoms. In these cases simple cleanliness and dusting with calomel powder suffice.

When should constitutional treatment be begun? The moment a positive diagnosis of syphilis can be made. The disease should be attacked too soon rather than too late; for when treated from its commencement it generally shows itself amenable to treatment, benign in its symptoms, and relatively less severe as regards later manifestations. The increasing difficulty of an absolute cure, as time advances after infection, has been abundantly proved by recent serological studies. On the whole, syphilis is more dangerous and less curable when treatment is begun late; early treatment often prevents many of the distressing and compromising secondary symptoms, and, if the diagnosis be made, "it is impossible," in the words of Hutchinson, "to commence too soon." But *only if the diagnosis be made;* for in cases in which careful examination of the lesion leaves one in doubt as to its nature it is better to wait until the appearance of confirmatory evidence. Previous to the work of Schaudinn and Wassermann a large proportion of the cases fell in the doubtful class. Physicians frequently found themselves compelled to waste precious time waiting for the evolution of symptoms sufficiently characteristic to warrant instituting the tedious and disagreeable treatment, which could not be undertaken and efficiently carried out if there was any doubt that the disease really was syphilis. At present, however, the nature of the initial lesion can be positively recognized, in most cases by finding the *Treponema pallidum*, and in the later stages a positive Wassermann reaction will give us the necessary information. In a large number of cases treatment therefore may be begun as soon as the patient is seen.

1. *Auxiliary Treatment.*—(*a*) *Diet.*—Many idle words have been written as to diet; and although the matter is by no means unimportant, it is simple and to be summed up in a few words. The keynote is the avoidance of excess. Irregularities of diet are to be forbidden and food and drink which cause diarrhœa or disturb the gastro-intestinal functions are to be avoided. Alcoholic excess is particularly dangerous. With these exceptions the diet should be interfered with as little as possible.

(*b*) *Hygiene.*—Here again avoidance of excess is the keynote. Overstimulation of an organ directs the syphilitic virus to that organ. Cerebral syphilis, for example, is especially common after nervous and

intellectual overwork, after excitement, dissipation, and venereal or other excesses. Again, buccal syphilides are most frequent and most serious in tobacco users. One should insist on the very great danger of overstrain to a syphilitic under treatment, and forbid tobacco.

Not an unimportant part of the physician's hygienic duty to his patient consists in attention to his state of mind. "Avoid sad passions" was the old advice to syphilitics; but, as Diday said, "Of all the anguishes, it is often the syphilitic anguish which lies heaviest on the syphilitic." This is the sad passion which the physician should correct. He can, fortunately, tell his patient, with truth, that the disease is curable, that safe marriage is possible, and that the prospect for healthy posterity is good. This wholly warranted assurance may be a very vital part of the treatment.

(*c*) Special attention must be paid to patients with *nervous predispositions*. It is the nervous system which is most often attacked by tertiary syphilis, and to these dangers nervous patients are more liable than others. It is the hereditarily neuropathic patients and the patients subject to nervous overwork who are especially subject to these calamities. Neurasthenia may be called one of the "localizing causes" of syphilis, and neurasthenic patients should be particularly careful in the avoidance of excess of every kind. Hydrotherapy and other more specifically neurasthenic treatment should also be used.

2. *Specific Treatment.*—Syphilis is one of the few infectious diseases for which therapeutic specifics are known; and in this instance there are four: mercury, bismuth, arsenic and potassium iodide.

Mercury.—Although its reputation as a specific has of late been overshadowed by the more dramatic effects of arsphenamine, and although it has probably lost permanently its preëminence in the treatment of syphilis, there is no reason to believe that the arsenical compounds will ever entirely supersede mercury. All the evidence at hand indicates that arsphenamine and mercury supplement each other and that together they are more effective than either drug alone. Mercury has been shown to possess distinct spirocheticidal qualities although these are less striking than are those of arsphenamine. The potency of mercury seems to be directly proportional to the amount taken up by the system. The drug is, at the same time, not without its injurious effects, and cannot be recklessly given. In the effort to combine the maximum of therapeutic effect with the minimum of untoward symptoms, several methods of administration have come into use.

(1) *Ingestion.*—This method is widely used, not because it is free from disadvantages, but because it is practical, in the sense that it is easy, convenient, and efficient. It has, however, the very serious disadvantage of not being suitable for the method of intensive treatment which at the present time is looked upon as being much the most affective. For this reason the oral administration of mercury has been largely replaced by other methods. Nearly all the preparations of mercury have been administered by the mouth, but the protoiodide and the bichloride have, after long experience, proved themselves most valuable. *Protoiodide* is insoluble and can therefore only be administered in the form of pills.

The dose varies from gr. $\frac{1}{6}$ to gr. j (0.01 to 0.06 gm.). A small dose of opium, gr. $\frac{1}{3}$ (gm. 0.02) is often prescribed with the mercury to prevent gastric irritation, the most famous combination of this sort being Ricord's pill.

Bichloride of mercury may be given either in pills or in solution. The usual dose for an adult is gr. $\frac{1}{16}$ (gm. 0.004) three times a day. This, too, is often combined with opium, to assure gastric tolerance, but the drug is preferably given without opium in pill form or in solution with a small amount of gum acacia. Sublimate solution is irritating to the stomach and should be given in a dilute form. On account of its objectionable taste and also to diminish gastric symptoms, syrup of sarsaparilla or peppermint may be prescribed with it. If taken in milk the drug is better tolerated by the stomach. The bichloride is often administered in solution, in combination with potassium iodide, in the form of "mixed treatment." If both drugs are needed, however, they should be given separately.

Gray powder (mercury with chalk) is a form of mercury particularly lauded by certain authors. It may be given in gr. $\frac{1}{2}$ (0.03 gm.) doses, and was Hutchinson's favorite form of treatment.

(2) *Inunction.*—This is the oldest of all the methods of administration of mercury. It consists in anointing the skin with salves containing the drug in a suitable form and in the olden days included, among other things, as an important part of the treatment, depuration by purgatives and bleeding. The ointment most often used is the well-known blue ointment, composed of equal parts of mercury and lard (double mercurial ointment, Neapolitan ointment). Lanolin may be substituted for the lard and is said to penetrate the skin better. Mercurial soaps have also been used, but, in spite of certain advantages, have not replaced the blue ointment. Mercury-vasogen (which may be had in 33 per cent., 50 per cent., and 75 per cent. mixtures, and should be ordered put up in gelatin capsules containing the required dose) is a clean and efficient form of ointment for this purpose. The average dose of mercurial ointment is 1 dram. For women, who are more subject to salivation from inunctions than men, $\frac{1}{2}$ dram is, as a rule, a sufficient dose. Infants tolerate inunctions well and proportionally larger doses may be prescribed for them; in quite young infants 15 to 30 gr. may be safely used. The inunctions should be carried out to the point of dryness; for a dose of 1 dram this requires at least thirty minutes. One inunction is usually prescribed per day for six days of the week; it is omitted on the seventh day, when a hot bath, preferably a Turkish bath or a sweat bath is taken. The hairy regions of the body should be avoided, as inunctions in these regions lead frequently and rapidly to stomatitis and often cause dermatitis. To avoid mechanical irritation, the seat of the inunctions should be varied, the sides of the thorax and the inner surfaces of the thighs and arms being chosen.

The inunctions are best given at night before retiring, the site of the application being covered with cotton, after rubbing, to prevent soiling and to keep the ointment from being wiped away. The inunction treatment is quite efficacious even when simply carried out; but a regular

sweating bath is beyond doubt of advantage, and life at a mineral spring, where hydrotherapy is practised, large amounts of water drunk, and frequent baths taken, make it possible for the patient to absorb larger amounts of mercury than can be taken up without such auxiliary treatment. The inunction treatment should be interrupted from time to time and a recess of a few days taken to avoid stomatitis, and the mouth, in all cases, should be carefully watched during the treatment.

(3) *Injection.*—The introduction of mercurials under the skin was originated by Hebra and Hunter, but it was first widely used after the publications of Lewin in 1867. The injections are best made into the buttocks, well above the ischial tuberosities, the two buttocks being used for alternating doses. An all-glass syringe is the best to use; the needle should be of sufficiently large calibre, and it is essential that it should be long enough to reach well through the skin and subcutaneous fat. The injections, although often spoken of as hypodermic, should be, intramuscular. The skin is washed with green soap and water and swabbed with ether. The needle is then plunged straight into the muscle, and watched for a moment to see that no blood escapes. If blood *does* escape, the needle should be reinserted. The syringe is then attached and the injection made. When the needle is withdrawn, a small collodion and cotton dressing over the puncture wound is sufficient.

Both soluble and insoluble forms of mercury have been used for this purpose. Of the former, bichloride, biniodide and succinimide; of the latter, metallic mercury, calomel, and salicylate of mercury have been the ones most frequently employed. The following are the formula:

Bichloride.—

Hydrarg. chlor. corros.	gr. j
Glycerini	ʒij
Aquæ destillat.	ʒij

Sig.—Injections of ♏v to xv every one, two, or three days.

Biniodide.—This may be given in a 0.4 per cent. solution in olive oil. The injections may be given every day, the dose at the start being ♏x, which is rapidly increased to ♏xxx or ♏l.

Metallic Mercury.—This is given as the gray oil, introduced by Lang, of Vienna. Half an ounce of mercury is rubbed up with 2 ounces of anhydrous lanolin, and the mixture then increased to 5 ounces by the addition of paraffin oil. Enough carbolic acid should then be added to make a 2 per cent. solution for antiseptic purposes.[1] This mixture should not be warmed, in which case the mercury separates out; nor cooled, in which case the solution stiffens. The dose is ♏x and the injections may be given once a week or once every five days.

Calomel.—This is given in glycerin, according to the following formula:

Calomel	gr. xxiv
Glycerin	ʒij
Distilled water	ʒij

[1] This is the principle, although not the exact formula, of Lang. The formula is the one recommended by Lambkin, of the British Army.

This may be sterilized by placing the bottle in which it is kept in boiling water and keeping it there for an hour. The dose is ♏v to ♏xv (gr. ½ to 1½) injected every five to fifteen days. Olive oil, oil of vaselin, oil of almonds, and distilled water may also be used for making the suspension.

Salicylate of Mercury.—This is best given as a 10 per cent. solution in liquid albolene, which may be sterilized by heating. The dose is ♏x once or twice a week. The injections usually cause no local disturbances, but indolent nodosities have been seen after the use of salicylate.

For the insoluble salts, 10 to 15 injections repeated at intervals of five to fifteen days constitute an ordinary course. The soluble salts must be administered more frequently; 20 to 30 injections, at intervals of from one to three days, are regarded as a course.

Certain authors have advised the use of massive doses of soluble salts of mercury. This is dangerous; for the rapid absorption, which is beyond control, may lead to alarming symptoms. Moreover, although intense mercurialization may be thus produced it does not appear that the influence of such injections on the disease is persistent.

Intravenous injection of mercurials, introduced by Bacelli, of Rome, has, in spite of its dangers, found certain staunch supporters. Bacelli used bichloride in 0.1 to 0.2 per cent. solutions, 1 cc. (representing gr. $\frac{1}{16}$ to gr. $\frac{1}{32}$) being injected. The therapeutic effects have not, however, been superior to those of other methods.

(4) The introduction of mercury by fumigation, by mercurial baths, and by mercurial plasters should be mentioned for completeness, though the methods have little more than historical interest.

Merits of the Various Methods of Mercurial Administration.—Ingestion is particularly appealing by reason of its simplicity. It is less liable than inunction to cause stomatitis, and the stomatitis which it causes is of a less rapid and severe type. It avoids the pain and occasional accidents of injection. The method is, on the average, best suited to the occupations, convenience, and social and professional obligations of the average patient; and the probability that convenience of form of treatment will make for prolonged and efficient treatment is not to be lost sight of. Patients who will not submit to inunctions or return for injections will swallow pills almost indefinitely. On the other hand cases which do not yield to ingestion sometimes clear up promptly when intramuscular injection are used. There is a growing conviction among syphilologists that the mouth administration of mercury has no place in the modern method of intensive treatment.

The chief advantage of *inunction* is its active therapeutic effect. This may be an absolute indication for the choice of this method where urgent symptoms are present. But the absence of gastric complications is an additional advantage. Again, inunction leaves the stomach free for other medication; either the exhibition of iodides, when mixed treatment is carried out, or the administration of auxiliary medication (potassium bromide, tonics, etc.). On the other hand, it is a dirty, inconvenient, and repulsive method, involves a certain amount of publicity, and often discourages patients, leading them to abandon treatment altogether. It is occasionally accompanied by diarrhœa and by dermatitis; and

quite commonly by stomatitis which occurs more frequently with this method than with any other. Moreover, the stomatitis which it causes is more rapid in its onset, more general and more intense in its manifestations than that seen after ingestion. Inunctions are also somewhat uncertain in their effects; one patient responds well to them, another badly. This is no doubt due to the way in which the rubbing is done, and for this reason the method is not always applicable. It cannot be too strongly insisted that patients who are receiving inunctions should be carefully watched, particularly as to the development of stomatitis; and that care should be taken that the rubbing is well done. The method is indicated in severe cases (cerebral and spinal syphilis), in cases refractory to other methods, in dyspeptics and those subject to diarrhœa, and in cachectic patients. It is of particular value in the treatment of syphilis in young infants, whose lives may depend on the integrity of the digestive system.

The method of *intramuscular injection* is a relatively accurate one. The drug must be administered by the physician, and deceit as to the amount of the drug taken is avoided. The chief advantage of the method is its therapeutic intensity; it induces mercurialization rapidly and intensely, and is of particular value in the presence of urgent symptoms. It also leaves the stomach free for other medication, and does not, as a rule, cause intestinal symptoms. It is claimed that the hypodermic method ensures the most exact dosage of mercury; but this accuracy is an apparent rather than a real one; for the sufficient dose of a drug is to be estimated not alone by the amount given, but by the physiological effects obtained, and these can be estimated quite as well when inunctions or ingestion are used. Pain and local irritation are strong objections; for, aside from the inconvenience caused, these are often sufficient to make the patients neglect treatment altogether. The formation of nodosities and sloughs is occasionally seen, although only rarely with present-day technique. The method is not wholly free from danger. Several cases of pulmonary embolism have followed the subcutaneous injection of calomel; and hemorrhage and nervous accidents (partial paralysis, trophic disorders, etc.), although rare, have occurred.

Intravenous injections may be given without pain. Local accidents are, as a rule, absent; the dose given is mathematically controlled; and much has been claimed, by enthusiasts, for the therapeutic results. As a rule, however, it has been generally abandoned, and is now recommended only when very rapid action is required.

Flumerin, the disodium salt of hydroxy-mercuri-fluorescein, is a new mercurial said to possess a relatively low toxicity and a much higher degree of spirocheticidal power than the mercurials in common use. It has been used only intravenously and produces little or no local irritation. The average adult dose is 0.25 to 0.3 gm., administered in a 2 per cent. solution every two or three days. Thus far its use has been too limited to make possible any trustworthy conclusions as to its value. Moore and Wassermann believe that its chief field of usefulness lies in the treatment of early syphilis in alternation with arsphenamine. In the later stages

of the disease it is doubtful if this drug has any special advantages over the older mercurials.

Mercury and the Wassermann Reaction.- In spite of the fact that the clinical results of treatment by mercury are frequently satisfactory or even brilliant the behavior of the Wassermann reaction is often such as to make it doubtful if cases so treated are actually cured; for most of the recent statistics bearing upon this point indicate that, as a rule, the reaction either remains positive in spite of the treatment, or, if rendered negative, soon becomes positive again after treatment has been discontinued.

The Disadvantages of Mercury.—Aside from the question of method of administration, the dangers of the drug itself must be considered. *Stomatitis* is the complication most frequently seen. This was formerly regarded as an essential part of the cure; in the days of Astruc "a good cure required a good salivation of 4 or 5 pounds a day." The stomatitis now observed, however, is usually of a milder type and begins as a gingivitis. The saliva becomes stringy and superabundant; there is a metallic taste in the mouth; the gums (especially of the lower jaw) become reddened and swollen and bleed easily; the teeth become tender and appear to the patient to be elongated. There is a metallic and fetid odor to the breath. In bad cases, not often seen, the entire mucous membrane of the mouth is swollen, ulcerated, and bleeding; ropy saliva wells from the lips; the teeth are exceedingly tender, become loose, and may even fall out. The ulcerations of the buccal mucosa may resemble mucous patches quite closely. Stomatitis may often be prevented by careful hygiene of the mouth. Neglected mouths are particularly subject to stomatitis, and mercury should never be given without inspection of the mouth. Where this is in bad condition, attention should be paid to it. But in any case the teeth should be carefully and regularly brushed and the mouth frequently washed with a solution of chlorate of potash or some astringent wash. The gums may be occasionally painted with tincture of iodine. Patients should be informed of the buccal accidents of mercury and told to report immediately if any symptoms are noticed. On the least sign of buccal irritation, mercurial treatment should be discontinued.

Salivation, when present, is treated, as follows: Stop mercurial treatment and order immediate and repeated Turkish or vapor baths. See that the bowels are kept open and that large amounts of water are taken. Order a potassium chlorate or potassium permanganate mouth-wash to be used every hour, and internal doses of potassium chlorate (5 gr. three times a day) for three or four days. Atropine in doses of gr. $\frac{1}{100}$ (0.00065 gm.) may be given. The gums may be painted with silver nitrate solution and tincture of iodine. In ulcerous stomatitis, hydrobromic acid or silver nitrate should be used to cauterize the ulcers.

Gastro-intestinal complications are not infrequent during mercurial treatment. These may take the form of pains in the stomach, colic, diarrhœa, loss of appetite, or even persisting dyspepsia. Some corrective (such as opium) will often suffice to prevent or attenuate these complications. But even the strongest stomach may become fatigued by the

remedy, and treatment should therefore be now and then suspended, to give the digestion a respite.

Disturbances of nutrition, in the form of languor, anemia, want of appetite, fatigue, and emaciation, occasionally occur, particularly when mercury has been too strenuously prescribed. The urine should be carefully watched and the drug stopped if any signs of renal irritation appear.

Cutaneous Complications.—Irritative dermatitis from inunctions is a local affair and may, by varying the site of inunction, be avoided. The absorption of mercury also causes eruptions. They are due to a personal idiosyncrasy and occur with even very small doses. The most common form is that of desquamative polymorphous erythema. In the milder cases, the symptoms consist only in local heat and itching, with slight fever. Occasional cases are severe, the clinical picture being that of a severe, extensive burn.

Bismuth.—Since the publication of the researches of Sazerac and Levaditi in 1922 much attention has been directed to the antisyphilitic action of bismuth. Its active spirocheticidal effects have been demonstrated both experimentally and clinically and the metal seems likely soon to win a position of equal importance to that of mercury and arsenic as an antisyphilitic remedy. The evidence indicates that in the treatment of syphilis bismuth is more effective and less toxic than mercury and is nearly, if not quite, equal in effectiveness to arsphenamine. Its toxic effects resemble those of mercury and are shown chiefly in the production of stomatitis, degeneration and necrosis of the renal tubules and colitis. Hopkins[1] concludes that bismuth should certainly be used in cases which are intolerant to arsphenamine and mercury, and in cases which have not responded to thorough treatment by these drugs. He thinks it advisable also that bismuth be used in the routine treatment of syphilis, replacing some of the courses of mercury. There is at present no evidence to justify the substitution of bismuth for arsphenamine. Several different preparations of bismuth have been employed and there is no unanimity of opinion as to the preparation of choice. Potassium and sodium bismuth tartrate (soluble) and precipitated bismuth (insoluble) are two of the better known preparations. The drug is administered by deep intramuscular injection into the buttocks. Usually it excites little or no pain but occasionally a painful inflammatory induration appears two or three days after injection which rarely may result in a sterile abscess. The average dose of either of the two preparations named above is 0.2 gm,. given at intervals of from three to seven days. A course usually covers a period of six or eight weeks and may either accompany the administration of arsphenamine or be given in alternation with courses of the latter drug.

Arsenic.—The galenical preparations of this drug have long been known to possess some therapeutic value in syphilis and have been used in certain of the chronic skin manifestations of the disease. Only recently, however, have the modern powerful organic compounds of arsenic been employed for this purpose. Several of these, especially sodium cacodylate and atoxyl, were experimented with before the advent of arsphenamine

[1] *Jour. Am. Med. Assn.*, 1924, **83**, 2087.

but were abandoned because of their toxicity when given in effective doses.

Arsphenamine (*Salvarsan*).—This synthetic arsenic compound was first produced by Ehrlich and shown to possess a specific toxicity for *Treponema pallidum* and other parasites. The chemical name is dioxydiamido-arseno-benzol, and it is used in the form of the hydrochloride of the sodium salt. Its value for syphilis was first shown by the experimental demonstration that its injection into a syphilized rabbit caused complete disappearance of the *Treponema pallidum*. The results of extensive clinical studies have demonstrated that arsphenamine, when used with proper precautions, is a drug of the greatest value in the treatment of syphilis. The specific power of the substance depends on the anchorage of the trivalent arsenic by chemoceptors of the parasites; this anchorage does not occur with preparations in which the arsenic group is completely satisfied. The hope of Ehrlich that this drug would effect a complete cure of syphilis by the total destruction of all spirochetes has not been fulfilled. It has proved to be extremely valuable as an abortive measure in the early stages of the disease.

Arsphenamine has been administered both intramuscularly and intravenously. The intramuscular injections, however, proved to be so painful and so prone to result in abscess formation that the drug is now given almost entirely by the intravenous method. The preparation of arsphenamine for intravenous injection, as well as the technique of the injection itself, is somewhat complicated and requires careful attention to all its details in order that the injection may be made safe and free from unpleasant complications. A description of the technique sufficiently detailed and explicit to make it a safe guide cannot well be given in an article such as this. The use of freshly distilled water for the solution of the drug and its careful neutralization by sodium hydroxide are two of the more important steps in the process of preparation.

Neoarsphenamine (*Neosalvarsan*), a modification of the original drug, was introduced by Ehrlich to obviate some of the disadvantages resulting from the complicated procedure required for the administration of Salvarsan. The technique of its intravenous use is much simpler than is that of arsphenamine in that it is more soluble, does not require neutralization and can be given in more concentrated solution. The action of the drug is similar to that of arsphenamine but as it contains only two-thirds as much arsenic its dose is correspondingly larger. By virtue of its ease of administration neoarsphenamine has been much used in ambulatory practice. As to the relative merits of the two preparations there is not yet complete agreement. Neoarsphenamine is unquestionably much easier of administration and gives less discomfort to the patient, but the weight of opinion at present supports the view that both the clinical and the serological effects of its use are less striking and satisfactory than are those of arsphenamine and that the latter drug is to be preferred. The precautions to be taken and the contraindications to the use of neoarsphenamine do not differ from those of arsphenamine.

Silver Salvarsan, the latest modification of Salvarsan, has been shown experimentally to be the most actively spirocheticidal and the least toxic

of the arsphenamine preparations thus far introduced. Although the published results of its use clinically have been decidedly favorable the drug has not yet come into very general use. The technique of its intravenous administration is quite similar to that of neoarsphenamine. It has been claimed for it that by its use the necessity for the administration of mercury is avoided. The average initial dose is 0.1 gm. and the maximum dose 0.3 gm., given by intravenous injection at intervals of from four to seven days.

Untoward Effects of Arsphenamine.—The local effects of both arsphenamine and neoarsphenamine are so irritating that their subcutaneous and intramuscular use has been almost completely abandoned. When given intravenously the slightest leakage at the point of puncture usually results in a sharp inflammatory reaction which may be accompanied by local thrombosis of the vein. The undesirable *constitutional* reactions to arsphenamine vary greatly in character. They may be immediate, intermediate, or delayed. Not infrequently certain vasomotor disturbances are noticed during the administration of the drug. There may be injection of the conjunctivæ, flushing of the face, a feeling of fulness in the head, tingling of the extremities, a peculiar taste in the mouth, and occasionally, precordial distress and tachycardia. Such symptoms, if troublesome, may usually be relieved promptly by epinephrine, given subcutaneously. The intermediate reactions, when they occur, are seen within the first twenty-four hours and usually within the first twelve. There may be headache, depression, malaise, chill, fever, nausea, vomiting or diarrhœa. Severe reactions are less common now than formerly. Certain patients are much more liable to such reactions than are others, but scrupulous care in the preparation and administration of the drug and the selection of a reliable preparation will do much toward reducing the frequency and severity of the symptoms.

Of much greater importance and seriousness are the delayed reactions which may appear at any time from two or three days to many weeks after the administration of arsphenamine. Among such reactions are to be included certain skin eruptions, irritation of the kidney, jaundice, and various cerebral manifestations. Skin rashes may be of urticarial, erythematous or purpuric character. Most important of these is the rare form of desquamative dermatitis which may involve the entire surface of the body and is always serious and not infrequently fatal. The urine often shows evidence of mild renal irritation and occasionally a severe nephritis may be found. Jaundice is a complication which may appear from one to two months after treatment and is commonly ascribed to direct toxic action of the drug upon the liver cells. Milian, however, has found that it usually occurs in those who have received insufficient treatment. There is always risk in giving arsphenamine to a patient with hepatic disease.

Much the most important of the late reactions to arsphenamine is the form of hemorrhagic encephalitis which has been the cause of more than half of all the deaths ascribed to the drug. The usual symptoms are headache, nausea and vomiting, vertigo, muscular twitchings, convulsions, and coma. Examination of the brain has shown scattered, punctate areas

of hemorrhage and softening, together with evidence of cerebrospinal syphilis. It is possible that in some of these cases the lesions may be the result of the direct toxic action of the drug or its impurities. The general belief, however, is that in most of the cases the damage is caused by the liberation of endotoxin from the rapid destruction of a large number of spirochetes. This phenomenon of increased activity in syphilitic lesions following antisyphilitic treatment and especially treatment with arsphenamine, is known as the Jarisch-Herxheimer reaction. When such increased activity occurs in lesions of the central nervous system the results may be most serious. The generally accepted explanation of the phenomenon is that given above, namely, that the symptoms result from the sudden release of toxins from the bodies of the destroyed organisms. While the total number of deaths following the administration of arsphenamine has unquestionably been large the percentage of mortality among the vast number of cases so treated has been very small. With the growing appreciation of the need for great care in the selection of a trustworthy preparation and in the technique of preparing and administering the drug, and with a better understanding of the proper dosage and of the contra-indications to its use, such fatal accidents are now extremely rare.

The list of contra-indications to the intravenous use of arsphenamine, at the present time, is much shorter than that given by Ehrlich. In severe nephritis, in the more advanced stages of syphilitic aortitis and pulmonary tuberculosis, and in cachectic states generally, the drug should not be used. In cases of active cerebrospinal syphilis and in early cases of congenital lues arsphenamine at first should be used cautiously and in small doses in view of the danger of a severe Jarisch-Herxheimer reaction. The danger of continuing the use of the drug in cases in which a dermatitis has appeared has been emphasized by Fordyce, who thinks that no further treatment should be given within six months or a year.

Clinical and Serological Results from Arsphenamine.—In the early stages of the disease the effects are often astonishingly prompt and striking. After even a single injection the spirochetes may disappear from the lesion within a few hours. Both the initial sore and the secondary lesions of the skin and throat usually heal with surprising rapidity. In the case of late visceral lesions the effects are less dramatic and the best results are secured by the combined use of arsphenamine, mercury, and potassium iodide.

The effect upon the Wassermann reaction of treatment with arsphenamine is most pronounced in the primary and early secondary stages, when, after even 2 or 3 injections, the reaction usually becomes negative within three or four weeks. Later in the secondary stage a longer course of treatment is usually required to change the reaction, whereas in the tertiary stage two or more courses of treatment may be needed to render the reaction negative. In a certain proportion of the cases indeed a permanently negative reaction may never be secured.

Potassium Iodide.—This drug takes a prominent place in the therapeutics of the tertiary stage. It is very soluble in water, rapidly absorbed, and appears in the urine twenty minutes after ingestion. The economy soon becomes impregnated by it and it may be found in all the secretions.

Its power to dissolve luetic tumors is one of the most dramatic things in therapeutics. The drug may be administered by the mouth, by the rectum, or hypodermically; but inasmuch as it is usually well tolerated by the stomach, the second two methods have little more than theoretical interest. In certain rare cases the administration by enemata might be indicated, as in unconscious patients in whom it was not desirable to pass a stomach-tube; but for all practical purposes the drug should always be administered by the mouth. It should be given in weak solution, as strong solutions have a disagreeable taste and irritate the stomach. The taste may be masked by giving the drug in milk or by adding peppermint or one of the syrups (the best is syrup of bitter orange). When the taste of iodide is persistently nauseating, one has to experiment until some pleasant drink is found which successfully masks it. The drug should be taken after or during meals. In some patients it causes constipation, in others diarrhœa; and a mild purgative or astringent should in these cases be prescribed with it.

As to the dosage, there is divergence of opinion. Some advocate small, others extremely large, doses. Fournier held that the method of beginning with small doses is bad, for it is the small doses which appear to be particularly harmful. On the other hand, he was strongly against what he calls "iodide debauches." He began, for an adult man, with 30 gr. daily (given in three doses); for a woman, with 15 to 20 gr. The dose is gradually increased until it reaches 45 to 60 gr. daily, and here it remains. When the indications are very urgent larger doses (beginning with 70 to 90 gr. and rapidly increasing to 150 to 180 gr.) are given; but doses of 500 gr. he regarded as useless "intemperance." When tolerance for the drug is established, the curative value apparently diminishes, and the dose must be increased. Other authors advise larger doses, beginning with 30 to 40 gr. daily and increasing a grain a day until about 250 gr. daily are given. Gottheil reports a case of gumma of the meninges which only showed improvement when 900 gr. were administered daily; half of this was introduced into the stomach through a tube and the rest into the rectum in enemata. Whether parasyphilitic affections would be prevented by routine employment of massive doses, as claimed by some authors, is still unsettled.

Iodide of sodium, ammonium, and rubidium, iodine, iodoform, and other iodine compounds have been used instead of iodide of potassium; but none of these has yet proved itself a satisfactory substitute.

In spite of the universally recognized value of iodine in the treatment of tertiary syphilis its exact mode of action has always been obscure. Both experimental and clinical evidence has shown that the drug is not a spirocheticide, that it has little or no effect in early syphilis and that it does not influence the Wassermann reaction. The experimental work of Jobling and Petersen suggests that its specific effect in producing the rapid absorption of gummatous deposits is due to its power of inhibiting the action of the anti-ferments. These normally interfere with the autolytic action of the ferments upon devitalized gummatous tissue.

Although iodine often plays such an important part in the treatment of late syphilis it is most effectively used in combination with mercury

alone or with mercury and arsphenamine, which provide the spirocheticidal action lacking in iodine itself.

Iodism.—Potassium iodide may have certain untoward effects. The occurrence of these symptoms seems to be determined by an idiosyncrasy of the patient. They appear after small doses and often early in the treatment. The most common are the iodic taste, coryza, and acne. The taste is a slightly salty or metallic one, is especially noticed in the morning, and is most frequent in women. The coryza is much like that of an ordinary cold in the head; it is characterized by snuffling, a sense of nasal obstruction, running from the nose, frontal headache, etc. The discharge from the nose is usually serous. The coryza may disappear in a few hours or last, in a subacute stage, throughout the treatment. The acne eruption generally appears on the face in the form of recurring crops of acneform pustules, seldom more than four or five at a time. Both the coryza and the acne may appear in severe form, the former resembling influenza and the latter appearing as a large, furunculoid, deforming eruption. Other rare symptoms of iodism are neuralgic pains, especially of the jaws, and most often seen in women; a mild sialorrhœa, never so intense as in mercurial salivation; conjunctivitis; iodic purpura; gastrointestinal symptoms (nausea, vomiting, diarrhœa); swelling of the salivary and parotid glands; and localized œdema, especially of the eyelids.

The eruptions of iodism, which are sometimes severe and occasionally fatal, appear in three general types; the bullous type (iodic pemphigus), the furunculocarbuncular type, and the pustulocrustaceous type. The latter may be impossible to distinguish from tertiary syphilides; the rapidity of invasion, the initial form of the eruption, the inflammatory character of the areola, the soft base, and the disappearance of the eruption on suppression of the drug make the diagnosis. Purpura may occur. Iodic œdema of the respiratory passages, sometimes requiring tracheotomy and occasionally ending in death, is another rare result of iodism which must be mentioned.

The accidents of iodism are not as a rule severe; the symptoms often disappear as tolerance is established, and suppression of the drug is not necessary. When they do not disappear, it may be discontinued for a short period. For patients who are subject to localized œdema and to prevent the nasopharyngeal accidents, belladonna may be exhibited, 1 gr. of the extract being given daily.

Method of Treatment.—Although the general principles underlying the modern treatment of syphilis have become well established there are still such great differences of opinion with respect to its many details that concise and definite statements concerning all of these are hardly possible. There is no difference of opinion, however, as to the fact that the prospects for complete and permanent cure are best when treatment is instituted in the primary stage of the disease, at which time the spirochetes, although widely disseminated by the blood and lymph streams, have not yet become fixed in the tissues. It is therefore of the utmost importance to the welfare of the patient that treatment be begun at the earliest moment possible and that it be carried out intensively and persistently.

During the primary and secondary stages arsphenamine and mercury (or bismuth) are the essential remedies and potassium iodide is of little or no value. In the late stage of the disease, on the other hand, the iodides are often of prime importance.

In dealing with the question of dosage consideration must be given to various factors, such as age, sex, weight, temperament, state of nutrition, stage of the disease and reaction to treatment.

In the early period the treatment should consist of several (three to five) courses of arsphenamine, or neoarsphenamine, and of mercury. Each course of arsphenamine should include from 4 to 6 intravenous injections given at intervals of from seven to ten days, the doses for men being from 0.3 gm. to 0.6 gm. and for women from 0.2 gm. to 0.45 gm. The first two doses should be considerably smaller than the subsequent ones. Each course of mercury should consist of 10 or 12 intramuscular injections of an insoluble salt, given at intervals of from five to ten days, or from 15 to 20 injections of a soluble salt, given at intervals of two or three days. Whether the mercury is best administered simultaneously with the arsphenamine or during the intervals between the courses of the latter is still unsettled. Each plan has its advantages and its enthusiastic advocates.

The length of the rest periods between the courses of arsphenamine is usually from one to two months, depending upon the behavior of the Wassermann reaction, the tolerance of the patient to the drug and his state of nutrition. If the Wassermann test becomes negative after the first course of treatment and remains so permanently, at least two further courses should be given before the patient is assumed to be cured. When the Wassermann reaction shows a tendency to remain positive one or more courses of bismuth should be substituted for those of mercury.

In the tertiary period, and especially when visceral lesions are known to exist, arsphenamine should be used cautiously and in small doses if at all. Chief reliance should be placed upon mercury (or bismuth) and potassium iodide. If arsphenamine be used it should be preceded by mercury alone or mercury and the iodide (Fordyce).

The serological results of treatment in the tertiary stage are much less satisfactory than in the early period of the disease. In many cases a positive reaction persists in spite of energetic and prolonged treatment. In such cases examination of the spinal fluid will often reveal evidences of involvement of the central nervous system even when neither physical signs nor symptoms are present.

Treatment of Syphilis of the Nervous System will be discussed under Diseases of the Nervous System.

Treatment of Congenital Syphilis.—To paraphrase a familiar saying, the treatment of congenital syphilis properly should begin many months before the child is born by treatment of the infected mother; and with the rapidly growing interest in the subject of antenatal study and care it is reasonable to expect that the incidence of congenital syphilis will steadily decrease.

The early form of congenital lues corresponds with the secondary stage of the acquired disease and early and thorough treatment of this form is

quite as important, and often quite as effective, as is such treatment in the acquired form.

The method of treatment developed by Fordyce and Rosen[1] has gained rapidly in favor and seems to be distinctly the best one thus far employed in the treatment of these syphilitic infants.

The plan consists of several courses of mercury and neoarsphenamine, each drug being given by deep injection into the gluteal muscles. If care be taken to see that there is no leakage into the sensitive subcutaneous fatty tissue the injections are said to be followed by very little pain and by no other unpleasant results. An ordinary mercury needle of 19 or 20 gauge, cut down to a length of from $\frac{1}{2}$ to 1 inch, is employed, and this may be provided with a broad, concave shoulder which fits over the buttocks and steadies the needle during the injection. If the infant be in very poor nutrition, it is well to begin with mercury alone until the general condition has improved. A course consists of from 6 to 8 injections each drug, given at weekly intervals, and should be followed by a rest period of from four to six weeks.

A soluble salt of mercury (the bichloride) is prepared in palmatin in order to favor slow absorption. The dose of the bichloride is gr. $\frac{1}{10}$ or $\frac{1}{8}$. The dose of neoarsphenamine for infants of from three to eight weeks is 0.075 gm., for those of from two to six months 0.1 gm. and for those of from six to twelve months 0.15 gm.

The treatment of older children with the late form of congenital syphilis does not differ essentially from that of adults in the tertiary stage of the acquired form.

[1] *Jour. Am. Med. Asso.*, 1920, **75,** 1385; *Arch. Dermatology and Syphilology*, 1925, **5,** 1.

CHAPTER XVI

FRAMBŒSIA TROPICA (YAWS)

By LEWIS A. CONNER, M.D.

Yaws, or frambœsia tropica, is a chronic infectious disease prevalent in many tropical and subtropical countries and characterized by an eruption of sluggish raspberry-like nodules upon the skin. It is common on the west coast of Africa and in certain other of the more tropical countries of that continent. It prevails in Ceylon, the Malay States, and Java, is found also in Burma and in southern China, but is rare in India. It is very common in the West Indies, in Guiana and in certain parts of Brazil, Venezuela and Colombia. The disease is prevalent in many of the islands of the south Pacific, such as Fiji and Samoa, and is found to some extent in the Philippines and in northern Australia. The history of yaws is obscure. It was well known to the West Indian planters in the seventeenth and eighteenth centuries and as there are authentic records of outbreaks of the disease on slave ships bearing negroes to those islands it has been assumed that the disease is of African origin. That much uncertainty should have existed as to the relationship between yaws and syphilis is nor surprising in view of their many resemblances. Proof as to their separate identity was offered first by Charlouis who in 1881 experimentally inoculated with syphilis a patient suffering from yaws. Since that time the distinction between the two diseases has become clearly established.

The causative agent is the *Treponema pertenue*, a spirochete very closely resembling that of syphilis, discovered by Castellani in 1905. This organism is found constantly in the skin lesions and has been recovered from the spleen, lymph nodes and bone-marrow.

The disease is transmitted usually by direct contact, but it seems probable that it may be spread also by carriers, such as flies and other insects. Unlike syphilis, yaws is rarely or never contracted through sexual intercourse. Inoculation takes place most frequently upon the lower extremities but may occur upon the lip, face, nipple or at any point at which the skin is broken. Overcrowding, filth and unclean habits are potent factors in the dissemination of the infection. No age is exempt, but most of the patients are children or young adults. The disease is never inherited nor congenital.

Pathology.—The lesion of yaws belongs to the group of infectious granulomata and is confined almost exclusively to the skin. The histological changes involve both the cutis and the epidermis. In the former the bloodvessels are dilated and tortuous and there is a diffuse infiltration first with polymorphonuclear and eosinophile leukocytes and erythrocytes and later with plasma cells. From the epidermis there is down growth of the epithelium of the interpapillary processes with hyperkera-

tosis of the covering epithelium. The lesion differs from that of syphilis in the more diffuse character of the cellular infiltration, in the absence of large multinuclear cells and of proliferation of the endothelium of the vessels and in the more pronounced proliferation of the epidermis.

Symptoms.—The disease is usually divided into three stages. After an incubation period of from two to four or more weeks, often marked by malaise, headache and slight fever, the *primary stage* begins with the appearance of a small nodule at the point of inoculation—the primary yaw or framboesoma. This is usually single but may consist of a cluster of small nodules. The lesion at first is dry, but later becomes moist and develops a thick, yellow crust beneath which an ulcer or large fungoid nodule forms. The primary yaw heals, after a period varying from a few weeks to a few months, leaving a whitish scar which later becomes pigmented. Not infrequently this primary stage is unrecognizable and the first distinct symptoms are those of the secondary stage. In from one to three months after the appearance of the primary yaw the characteristic *skin eruption* appears, preceded usually by pronounced constitutional symptoms, such as headache, fever, malaise and muscular and rheumatoid pains.

The eruption at first consists of many small rounded papules, widely scattered over the exposed portions of the body. Most of the papules become capped with a yellowish point or crust. Some of these papules prove abortive and subside without further development while others increase in size and coalesce, forming large nodules which vary from the size of a pea to that of a walnut. These nodules soon become covered with a thick, yellowish or brownish crust. When this is removed or becomes separated there is exposed the bright red, moist granulating surface of the fungoid masses which constitute the typical raspberry-like nodules of the secondary stage. In the colored races these nodules are surrounded by a deeply pigmented areola. These secondary yaws, if untreated, persist for a period varying from a few weeks to several months and gradually heal by cicatrization. The lesions are rarely painful but are apt to cause troublesome itching. The scars usually become deeply pigmented. While the upper and lower limbs and the face are the parts most commonly affected, almost any part of the body may be attached.

Beside the typical raspberry yaw other types of skin lesion are seen. The small nodules especially about the mouth and arms may be arranged in circular form with healthy skin in the centre (*ring-worm yaws*). Some of the nodules instead of cicatrizing in the usual way may break down and form sluggish, chronic ulcers. On the palms and soles the lesions form flattened papules beneath the dense, thickened epidermis which may leave characteristically pitted scars. Lesions of the mucous membranes are not common but nodules are sometimes found at the base of the tongue and whitish patches (leukoplakia) may cover the dorsum. A more or less general enlargement of the lymph nodes is common. Fever and other constitutional symptoms are lacking as a rule. The general health is not impaired. Occasionally one or more of the large joints may become swollen and tender, and attacks of periostitis, especially of the digital phalanges, are not uncommon.

In most instances, with the termination of the secondary stage, the disease ends; the usual duration being from three to six months for children and from six to twelve months for adults. In badly nourished and feeble individuals, however, the manifestations of the secondary stage may be prolonged almost indefinitely. A *tertiary stage* is described by most writers. The lesions consist chiefly of gummatous-like nodules and irregular ulcerations which upon healing leave dense disfiguring scars. The disease known as gangosa, in which there is extensive ulceration and scarring of the nose, palate and pharynx, is now believed to be a tertiary manifestation of frambœsia. This tertiary stage is seen in only a minority of the patients and is much less important than the corresponding stage in syphilis. Lesions of the heart and arteries, of the central nervous system and of the other viscera are conspicuous by their absence.

Diagnosis.—In countries in which the disease prevails, this usually causes little difficulty. Chief reliance is to be placed upon the raspberry-like nodules of the skin, covered for the most part by thick, yellowish crusts. *Syphilis* is the disease most likely to be mistaken for yaws but a careful study of the history of the case as well as of the lesions should prevent confusion. Unfortunately, the Wassermann test is of little aid in differentiating the two diseases, since with the usual alcoholic antigen the reaction is positive in most cases of yaws. When an aqueous extract is used as antigen the reaction is said to be usually negative.

Prognosis.—Frambœsia is rarely, if ever, the direct cause of death. Nevertheless it produces a long period of invalidism and disability and is an economic factor of much importance in countries in which it is prevalent.

Treatment.—The results of treatment by arsphenamine and neoarsphenamine have been most satisfactory. A single course of three or four intravenous injections usually affects a complete and permanent cure. Neoarsphenamine has been the drug usually employed. The dosage does not differ from that used in syphilis. Mercury is said to be of little or no value. When the arsenicals are not procurable or their employment not practicable Castellani advises the use by mouth of large doses of potassium iodide and tartar emetic. The open skin lesions should be washed with some disinfectant lotion and covered with a protective dressing to lesson the chances of transmission of the infection.

For a fuller discussion of frambœsia, with instructive illustrations of the characteristic skin lesions, the reader is referred to the article by Castellani and Chalmers in the *Practice of Medicine in the Tropics*, Byam and Archibald. London, 1922, vol. 2, p. 1306; and that by Plehn in *Handbuch der Tropenkrankheiten-Meuse*, 2d Ed., 1914, vol. 2, p. 275. In the latter will be found a very complete bibliography.

CHAPTER XVII

THE RELAPSING FEVERS

By JOHN L. TODD, M.D.

Synonyms.—English, Relapsing Fever, Famine Fever, Spirillum Fever, Remittent Fever, Recurrent Typhus, Tick Fever, Bilious Typhoid; Latin, Febris Recurrens; French, Fièvre Récurrente, Fièvre à Rechutes; German, Typhus Recurrens, Hungerpest, Ruckfallfieber.

Attempts have been made to distinguish several relapsing fevers. It is true that there may be differences in the morphology of the spirochetes, in the symptoms of the diseases which they produce, and in their methods of transmission; but their similarity to one another is so great that it seems wisest to describe relapsing fever as a single disease which may be modified, in various ways, both in its method of transmission and in its course.

Definition.—Relapsing fever is a febrile disease caused by a spirochete and characterized by an intermitting fever; it is transmitted, as a rule, through the agency of a tick or a louse.

Etiology.—In 1868, Obermeyer, in Berlin, saw spirochetes in a patient's blood, but did not publish his observation until 1873, when it was quickly confirmed in many parts of the world. In 1874 Lebert named the parasite *Spirochæta recurrentis*. The work of Carter, in India, and of others proved, by injecting infected blood into healthy persons—as well as by accidental infection at autopsies—that relapsing fever could be reproduced in men by inoculation; it also showed that spirochetes would live and multiply in the blood of monkeys, mice, rats, and, to a less extent, in the blood of other animals. The prevalence of relapsing fever among persons living in crowded, verminous quarters suggested to many (Flügge, Tictin, and Karlinski) that bed-bugs, lice, or fleas might be able to transmit it; but none of the attempts to transmit the disease by their bites has been successful with the exception of one (Nuttall). In this experiment bugs which had partially fed upon an infected animal were allowed to finish their feed on a susceptible one. It has, however, become certain, through the observations of Mackie (1907) and of Sergent, and Nicholle (1912) and their collaborators, that relapsing fever is often contracted through scratching which crushes infected lice and rubs them into the scratches. The last named observers also showed that lice hatched from eggs laid by infected lice are themselves infected. In 1904 Ross and Milne found spirochetes in patients suffering from tick fever. Dutton and Todd (1904) made the same observation and showed that the spirochetes could be transmitted by a tick (*Ornithodoros moubata*) and that the infection was carried, through the egg, from one generation of ticks to the next.

Since 1905, when ticks (*Ornithodoros moubata*) infected with *Spirochæta duttoni* were brought to Europe, much work has been done on the African, European, Asiatic, and American forms of relapsing fever. Novy and Knapp and Breinl and Kinghorn showed that a strong immunity against spirochetes existed in laboratory animals which had recovered from a spirochetal infection; that a partial immunity to reinfection existed in men had already been observed clinically. Dutton and Todd (1907), Breinl, and Carter and Leishman (1909) showed that *S. duttoni*, both in ticks and in men, produces certain granules which, probably, are a stage in the development of the parasite. In 1911 and 1912 it was shown that Ehrlich's salvarsan and neosalvarsan are specific in the treatment of relapsing fever. In 1912 Noguchi grew spirochetes on a culture medium.

Distribution.—Relapsing fever occurs, or has occurred, in almost every part of the world where men live in verminous squalor. Because the vermin—ticks and lice—which transmit the disease, are distributed by infected men as they travel, relapsing fever is especially likely to appear at points along the main routes followed by the traffic of the world. This has been especially well seen in the introduction of tick fever into Africa; its distribution there marks out the lines of travel followed by the natives of Zanzibar. Though relapsing fever is less prevalent in Europe than it once was, cases are still occasionally seen in Ireland, Norway, and Denmark, and many cases occur annually in Russia, Poland, Southern Austria, and Turkey. Relapsing fever is endemic in many places in the North of Africa and in Asia Minor; tick fever may exist almost anywhere in Central Africa.

Relapsing fever has been described in many parts of Asia; it is endemic in India, in Indo-China, and in parts of China. A fever carried by a tick (not *Ornithodoros moubata*) and probably caused by a spirochete occurs in Persia.

The disease is not endemic in North America, though cases are often seen, usually among recently arrived immigrants. It has been observed in several places in Central America and it is probably more widely distributed there and in South America than is recognized.

Spirochetes.—The spirochetes are very easily inoculable, and if infected blood or other material be touched they will find their way into the body through the smallest injury to the skin, or even through the unbroken epidermis; consequently, many persons have been accidentally infected in autopsy rooms and in laboratories.

Normally, the spirochetes are transmitted through the agency of an arthropod; ticks do so in many parts of the world. In Central and Eastern Africa "tick fever" is carried by *Ornithodoros moubata;* in Northern Africa and Asia Minor *O. sarignyi* and *Argas persicus* (probably) are vectors; further East, in Persia and India *O. tholozani* transmits the disease. In Central America *O. turicata* and *O. talaje* are carriers of relapsing fever. When the part played by ticks in the transmission of tick fever became known, attempts were renewed to transmit other forms of relapsing fever by the bites of the vermin infesting the populations among whom these diseases exist. Animals infected with various spirochetes of human origin were subjected to the bites of bed-bugs, fleas,

head-lice, and body-lice. After an interval of a varying number of days the vermin were allowed to feed upon healthy, susceptible animals. None of them became infected as they would have done had the ticks which transmit relapsing fever been allowed to feed upon them in the same way. Only once have spirochetes been transmitted by the bites of bed-bugs; in that instance the infection was probably carried mechanically on the mouth parts of the bugs which were partially fed on an infected animal and then allowed to finish their meal on a healthy one (Nuttall). Examination of lice and bugs fed upon infected animals shows that spirochetes can live in the alimentary canal of bugs and lice long after the feeding at which they were ingested; moreover, it has been proved, by inoculating them into susceptible animals, that these spirochetes are infective. It has been shown, also, that susceptible animals and men become infected if lice, *Pediculus corporis* and *P. capitis*, which have previously fed upon blood containing spirochetes, are crushed and their bodies rubbed into scratches, such as those made by lousy persons in scratching themselves. It is probable that this is a usual method of acquiring the disease.

Long-known peculiarities of the distribution of relapsing fever are easily understood when it is known that it can be transmitted by lice. During epidemics of relapsing fever in Russia, those who frequent vermin-infected, public night-refuges are very likely to contract the disease. In an Indian epidemic among school children many more boys than girls were attacked; the boys were much the more lousy. Doctors and nurses in relapsing fever hospitals rarely contract the disease, while those who come in contact with the patients before they are cleansed, or while they are wearing their soiled clothing, may be infected.

It was assumed, at first, that the ticks transmitted the spirochetes by their bites. At present, some doubt whether they do so; for it is possible for them to transmit infection in another way. Soon after an *Ornithodoros moubata* or an *Argas persicus* commences to feed, it excretes a considerable quantity of clear fluid, probably derived from the blood ingested; the fluid issues from the coxal glands, which are placed just behind the first pair of legs. Sometimes a small amount of thick, whitish excrement is passed at the same time by the anus. A fair amount of the clear coxal fluid, often 0.1 cc., may be voided by a large tick, it dilutes the thick anal excretion and the mixed excretions run between the tick and the host on which it is feeding so that both are smeared with them. Active, living spirochetes have been found in the mixed fluids, and it is quite conceivable that these organisms, as well as the coccoid stages of the spirochetes—which are said to be found in both the coxal fluid and in the anal excretion—may pierce the skin or find their way to the wounds made by the mouth parts of the ticks, and so infect the animal fed upon. Some assert that the bites of infective ticks will not infect susceptible animals unless they void excreta while they feed; this is denied by Marchoux and Couvy (1912) for *Argas persicus* and *Spirochæta gallinarum*. Certainly, this method of infection, though it is not necessarily the only one, makes it possible for ticks to transmit spirochetes.

The progeny of an infected tick are infected and capable of transmitting spirochetes for, at least, three generations; lice hatched from eggs produced by infected parents are also infective. An infected tick may retain its infectivity for an indefinite period even although it feeds only on uninfected persons; nevertheless, not every tick is infective; it is said that ticks may become immune to spirochetes and that it is then impossible to make them infective by feeding them on infected blood.

The spirochete, *Spirochæta duttoni*, which causes African tick fever, has been studied with more minuteness than any of the spirochetes causing other forms of relapsing fever. A description of its morphology and development will serve, in main part, for all of the pathogenic, blood-inhabiting spirochetes of man. This spirochete is a filiform organism, measuring about 14μ to 20μ in length and 0.2 μ in width; it is said to be slightly broader than the spirochetes of European relapsing fever. Its body is disposed in a number of waves so that it has the appearance of a spiral thread—hence its name; but if fresh and stained preparations are carefully examined, it will be seen that the spirochete is more like a ribbon than a thread, since its cross-section is flattened, and that it is not a true spiral, since its waves lie practically in one plane. It is actively motile, and progresses, with either end foremost, both by lashing movements of the whole parasite and by a "corkscrew motion" in which the waves move along its body and the whole parasite rotates along its longitudinal axis. Two, or several, spirochetes may be joined together end to end and in very heavily infected blood they may agglomerate in huge clumps or in hair-like tresses. In fresh preparations the substance of the spirochetes is usually homogeneous and it is difficult to distinguish the details of their structure. By appropriate preparation and using the highest magnifications it is seen that a spirochete consists of a thin outer coating, or periblast, and a central core. The periblast stains pink by Romanowsky's method, or its modifications, while the core stains a deep purple color resembling that taken by chromatin. Usually this chromatinic core is unbroken, but not infrequently there is a small break in it which appears as an unstained spot in the spirochete. When it exists this spot occurs most often at the junction of the central with a terminal third of the spirochete. The periblast may be effilated at either extremity and it may extend for some distance beyond the end of the core; these thread-like ends have been described wrongly as flagella. There are no lateral flagella. In many spirochetes appearances may be seen, by careful examination, which suggest that a very fine and narrow undulating membrane is wound spirally about them; but it is uncertain whether such a membrane exists. Although spirochetes may multiply in the peripheral blood by splitting longitudinally they usually divide transversely. Transverse division occurs at those thinner portions of a chain of spirochetes, joined end to end, which seem to consist of periblast only. Spirochetes which are about to divide transversely are longer than usual, those dividing longitudinally are thicker; so that there may be a good deal of variation in the morphology of the spirochetes in a single preparation. The chromatinic cores of spirochetes taken from the blood of persons who are near the crisis of an attack are especially liable

to be fragmented into several rod-like or granular masses; spirochetes with large granules attached to them either laterally or terminally, or with terminal club-shaped swellings, are not uncommon in blood examined at this time.

Spirochetes coiled up in a compact skein are occasionally seen in the blood; they are common in smears made from the organ juices—liver, spleen—of infected animals. Coiled spirochetes are especially numerous in the organs of subjects which have died just before the spirochetes have disappeared from the peripheral blood at the crisis of an attack. The chromatin of coiled spirochetes is usually, but not always, fragmented. Spirochetes, whether coiled and fragmented or not, are often found within endothelial cells in various organs and within phagocytes in the circulating blood. Rarely, and especially in the organs, they are seen within red blood cells.

If blood taken from the alimentary canal of a tick which has fed some time previously on an infected animal be examined, some of the spirochetes contained in it will be normal in appearance; the chromatinic core of others will be much fragmented and many will be coiled in skeins. Often, the coiled spirochetes are enclosed in a lightly staining matrix; similar forms may be seen in films made from the organs of infected animals. The chromatinic material of a spirochete, coiled and encysted in this way, may be disposed irregularly in short rods or granules, within the matrix, so that it is difficult to recognize that they result from the fragmentation of a spirochete. Spirochetes, altered in this way or normal in appearance, may be found within the alimentary canal and Malpighian tubules and oviducts of an infected tick. They may also occur within the cells of these organs, or in the connective tissue and muscle (Wolbach, 1913).

It is uncertain whether granules formed in this way are the result of a degenerative or regenerative process; but it is possible that they, and perhaps the larger terminal and lateral granules, sometimes attached to the spirochetes, may be infective. They are said to multiply by division. They occur in the ova and in the coxal and anal excretions, and the infectivity of these fluids and of young ticks, hatched from the eggs of infected parents, may be due, in part at least, to them. Similar granules have been seen in the spirochetes of fowls, and fragmentation of the chromatinic core frequently occurs in several other spirochetes; that both are common occurrences seems an additional reason for believing that both may be developmental processes.

The morphology of the spirochete, as described, is that which can be observed in preparations which have been dried, fixed in alcohol, and stained by a modification of the Romanowsky method. It is mentioned with full appreciation that complete significance cannot be attached to observations made on preparations prepared in this way until they have been controlled by the examination of fresh material and of preparations made by more perfect methods.

Some authors state that the spirochetes of relapsing fever are filterable and they suggest that the coccoid forms, described above, may be concerned with the production of the filterable form of the spirochete;

nevertheless, it is very doubtful whether any stage of these spirochetes can be said to be filterable in the usual sense of that term.

The spirochetes (*S. gallinarum*) of fowls, ducks, and geese, and other birds causes a fatal disease in them; it is transmitted by a tick (*Argas persicus*). Apparently non-pathogenic spirochetes have been found in the blood of cattle, bats, rats, mice, and fish; the way in which they are transmitted is not known. Spirochetes are often associated, usually in the tropics, with chronic or acute ulcerations of the skin, and at least two spirochetes are frequently parasites about the teeth of men in all parts of the world. All of these, with *Treponema pallidum*, and many free-living, non-pathogenic organisms, are closely allied, by their morphology, with the spirochetes of relapsing fever.

There has been much discussion concerning the systematic position of the spirochetes and, especially, whether they are to be classed with the protozoa, with the bacteria, or in a third kingdom distinct from either of these. The question is not yet decided, but at present the weight of opinion is that they should be placed near the bacteria.

Attempts have been made to distinguish several species among the spirochetes which cause relapsing fevers. These attempts have been made because of slight differences in morphology and pathogenicity for men and animals and because of numerous experiments in which animals refractory to one spirochete are shown to be immune to others. The attempts to distinguish species by slight differences in length, or by the number of waves in their bodies, are absurd, since slight variations in size may occur in a single species and the number of waves in a spirochete depends, largely, upon the way in which the preparation containing it has been made. Although there may be differences in the pathogenicity of different spirochetes and in the immunity resulting from infections, the most useful view to take is that these differences only constitute variations of a single species, *Spirochæta recurrentis*, and that this spirochete may be transmitted by various blood-sucking arthropods. From a practical point of view it would be useless to distinguish several relapsing fevers when the symptoms, treatment, and prophylaxis of all are practically identical.

The Vectors.—As a rule, the relapsing fevers are contracted through the intermediation of lice or ticks. Ticks[1] belong to the order *Acarina*; they and other members of this order transmit other diseases besides those caused by spirochetes. Ticks of various species and habits are parasitic on men, and on other mammals, birds, and reptiles in all parts of the world. The ticks which transmit pathogenic spirochetes belong to the family of the *Argasidae*, which have no scutum, their mouth parts are not conspicuous when they are looked at from above, and their habits are not like those of other ticks but resemble those of a bed-bug.

It has been said already that *Argas persicus* transmits *Spirochæta gallinarum;* it is also a vector of relapsing fever in Persia and in India. Ticks of this genus have no eyes. They are oval in shape and brownish-red in color. They are frequently found about chickens in parts of the southern United States.

[1] A *Monograph of the Ixodoidea*, by Nuttall, Warburton, Cooper and Robinson, University Press, Cambridge, is a very complete work.

In Africa, *Ornithodoros moubata* is the vector of tick fever. During the day this tick remains hidden in the cracks and crannies of a native hut or in the sand of its earthen floor. At night it comes out, finds its way, probably by smell, to those sleeping in the hut and sucks blood from them. Its bite causes little irritation. Usually, it is nothing more than a wheal, rather smaller than that caused by a mosquito's bite, with an obvious wound surrounded by a zone of ecchymosis at its centre. If a tick is disturbed it sometimes tries to escape but usually feigns death. A tick may feed for two or three hours before being satisfied and then is so distended that its skin is quite smooth instead of wrinkled as it was when feeding commenced. Although the ticks will feed almost every fortnight, if given an opportunity, they can live for many months, even years, without food.

Lice have six legs; they are, therefore, insects. There is a distinct louse for almost every animal; their distribution is universal. The body-louse and the head-louse may be vectors of *Spirochæta recurrentis.*

Pathology.—There is some jaundice and there may be petechiæ, submucous in the mouth, and subserous in various organs; but the most striking feature is a great increase in the size of the liver, and especially of the spleen. The spleen is soft, congested, and hyperplastic. All of the organs are hyperemic and the marrow of the long bones may be red. There is often marked cloudy swelling of all the organs, and there may be fatty degeneration of the heart, liver, and kidneys. Similar changes are seen in experimental animals; in sections of tissue from them, spirochetes can often be seen within the endothelial cells. In the spleen and liver, especially, fragmented and unfragmented spirochetes are often found within phagocytes.

Symptoms.—The length of the *incubation* period may vary between two and twelve days; the first attack usually commences in less than seven days after an accidental infection. There are often indefinite prodromes, malaise, headache, unusual perspiration, for a day or two before the onset. This is usually sudden with pains in the muscles and the back, characteristic, intense pain in the long bones, and headache. The temperature rises rapidly, sometimes with a chill, to 103° or 104° F. or even higher. With the fever is a pulse of 115 or more, rapid breathing, thirst, flushed and tender skin. The tongue is coated, anorexia is complete, and there is often slight nausea and vomiting. There may be constipation or diarrhœa, or both in succession. The temperature remains high, with slight morning remissions, until from the fourth to the seventh day, when it falls by crisis within a few hours to normal or below; it often remains subnormal for a few days after the attack. A very profuse perspiration accompanies the crisis. Although the attack leaves the patient weak he feels wonderfully well. A sudden death from heart failure may occur at the crisis in elderly patients and in those who are weak. During the attack the spleen and liver are enlarged, often painful and tender. The patient's skin becomes yellowish; in some epidemics jaundice is general and a well-marked feature of the disease. There may be a macular eruption; occasionally there are submucous pectechiæ in the mouth. Both hemoglobin and red cells are reduced, and there is

a polymorphonuclear leukocytosis. The urine is diminished and is often albuminous. Epistaxis, herpes, hiccough, iritis, and retinitis may be complications. Delirium is often seen in severe attacks; meningitis and paralysis are rare. Pneumonia and bronchitis are not infrequent.

During the interval the spleen and liver diminish in size, the patient's strength returns rapidly and he feels well. But in about eight days from the crisis there is almost always a second attack of fever, usually less severe than the first, but with the same symptoms. There may be from three to six, or even seven or more, attacks of fever, with intervening periods of apyrexia, before the illness ends. In the European form of the disease there are rarely more than two febrile periods. In fatal cases there may be no fall in the temperature and the spirochetes may increase steadily in numbers until the patient dies of toxemia. As a rule, pregnant women abort and deliver a still-born child. This description will do for all of the relapsing fevers, though there are differences between them. In the European form of the disease both pyrexial and apyrexial periods are rather longer than in the African.

During the attack the spirochetes can be found in the blood in increasing numbers. As a rule, the more severe the attack the more numerous the spirochetes; but they are said to be less numerous in African tick fever than in other relapsing fevers. With the crisis they disappear from it; but a very prolonged search will reveal them in peripheral blood taken during the interval and a susceptible animal can be infected by the inoculation of blood drawn from a patient at that time. The usual fate of the spirochetes circulating in the blood at the crisis is not known completely. Many of them become encysted in the cells of the liver, spleen, and lungs; others are engulfed by phagocytes.

The nature of the mechanism by which spirochetes produce the symptoms of relapsing fever is uncertain; but they are probably caused by a toxin produced by the spirochetes. It is unknown whether the recurrent course of the fever is due merely to periodical accumulations of such a toxin or, as is the case in malaria, to the repetition of some causative event in the developmental cycle of the parasite. With the first alternative the spirochetes may disappear because of the production of antibodies by the patient; the second, and more probable, explains both the febrile attacks and disappearance of the spirochetes.

Immunity.—An immunity results from an attack but its degree varies and persons may be twice infected in a single winter. Africans who live in a tick-infested region often suffer so little from relapsing fever that they declare the ticks to be harmless; but natives who go to that region from districts where there are no ticks, contract tick fever at once. It is suggested that the immunity of natives who are constantly exposed to tick bites may be maintained by frequent reinfection.

Diagnosis.—An absolute diagnosis depends upon the demonstration of spirochetes; they must be seen under the microscope. Although they may be easily seen, if they are numerous, in a fresh preparation, they are best found if they are rare, by the examination of a thick, dehemoglobinized film of blood. A large drop of blood is placed upon a slide and smeared over an area of about 1 cm. square. The blood is allowed

to dry and the preparation dehemoglobinized in water and fixed in absolute alcohol; or it may be dehemoglobinized and fixed by placing it in 90 per cent. alcohol, to which hydrochloric acid has been added, in the proportion of 1 drop to 5 cc., and then washing it in running water to free it from acid. After drying, the preparation is stained by any nuclear stain. Carbol fuchsin or methylene blue will do; but the best is one of the modifications of Romanowsky's method, such as Giemsa's. A Romanowsky stain should be used because other parasites, such as that of malaria, are well stained by it.

All of the hemoglobin is removed from slides prepared in this way, and the red cells become unstainable, so that, in a well-made preparation, nothing is seen but the nuclei of the white cells, a small amount of débris, perhaps a few basophilic red cells, the blood platelets, and any parasite that may be present.

It may happen that spirochetes cannot be found in a patient who is examined during an apyrexial period. In that event a drop of blood from the suspected case may be mixed with a drop of blood containing spirochetes taken from an infected person. The mixed blood is placed on a slide under a cover-slip, ringed with paraffin to prevent evaporation, and placed in an incubator at 37° C. After half an hour, the spirochetes should be clumped together if the suspected patient has relapsing fever (Löwenthal).

If there is any difficulty in finding the spirochetes, at least 25 cm. of blood may be taken from a vein, mixed with sodium citrate solution and injected into a young rat or into a monkey. Blood from the animal inoculated should be carefully examined twice daily for ten days before assuming that it has not become infected. If none of these methods can be employed, the clinical course, with its characteristic, relapsing fever, will be sufficient to justify a diagnosis.

Relapsing fever may easily be complicated by other diseases; the method by which it is transmitted is proof that those suffering from it have been living under unsanitary conditions. In the tropics, relapsing fever is often mistaken for malaria. In instances when a diagnosis is attempted without a microscope, the fall of temperature at the crisis is sometimes accepted as a "therapeutic proof" that the fever, for which quinine had been given, was malarial.

Prophylaxis.—Attempts to control any of the diseases transmitted by an invertebrate host may be directed primarily against the parasite causing the disease or against the vector which transmits it. Salvarsan and neosalvarsan are such efficient destroyers of spirochetes that relapsing fevers may be expected to disappear from areas where these drugs are persistently used in the treatment of the disease. Infected persons should be given neosalvarsan as soon as possible to destroy the spirochetes in them. They should be cleansed and isolated, so that vermin may have no opportunity of feeding upon them, nor of passing from them to healthy persons. The clothing of infected persons should be sterilized, and beds and rooms, occupied by them, should be thoroughly disinfected to destroy all vermin. During an epidemic those in contact with cases should be freed from vermin in order that they may not infect ecto-parasites, should

they have been infected, before the disease declares itself in them; they should be watched carefully so that cases may be isolated and treated at the earliest moment possible.

Those who are in localities where relapsing fever exists should take every precaution to avoid being bitten by ticks, bugs, and lice. In Africa, *Ornithodoros moubata* has been found on the veldt, on wart hogs and in their burrows. In Panama, *O. talaje* occurs on rats. But, as a rule, the ticks which carry relapsing fever are found only in the houses of natives or about old camping places. Such spots should be avoided; it is much safer for travellers to clear a space and camp in the bush.

It is possible to infect animals of several species with each variety of *Spirochæta recurrentis;* but no instance has been recorded in which animals have been found to be naturally infected. Consequently, it is not necessary, as in the prevention of trypanosomiasis, to institute measures for the destruction of animal reservoirs from which the invertebrate transmitters of relapsing fever might become infected.

It is unknown whether spirochetes survive from one epidemic of relapsing fever to the next in a free form, in animal hosts, in invertebrate hosts—lice and ticks—in which the spirochetes may be transmitted from generation to generation, or in men—either in occasional, atypical cases which escape recognition or as harmless, tolerated parasites.

Prognosis.—The disease is not serious in strong persons who are well cared for, but the mortality in some epidemics may be large; because, from its method of transmission, it is especially liable to occur among miserable and ill-cared-for persons whose power of resistance is small. The death-rate, under the old methods of treatment, in strong, well-cared for patients, was about 2 per cent.; but under adverse conditions, might reach from 10 to even 50 per cent. In fatal cases a secondary infection is often the immediate cause of death, but death may result from the toxemia of an intense infection or from collapse after a crisis. In persons properly treated by modern methods the mortality should be negligible.

Treatment.—This, like that of syphilis, has been revolutionized by the discovery of salvarsan as previously the treatment was entirely symptomatic. Baths and sponging were used to reduce high temperatures. Phenacetin and aspirin or opium were given for headaches and bone-aches, and purges were prescribed on general principles. Strychnine, ether, and other stimulants may be useful in cases of collapse; elderly or weak patients should be cautioned against excitement or active movement after a crisis.

Several unsuccessful attempts have been made to utilize the marked immunity, which can be acquired against spirochetes, in producing a serum which might be used in the treatment of the disease.

Ehrlich's salvarsan is a specific in the treatment of experimental and clinical infections by *Spirochæta recurrentis, (sensu latiore)*. Salvarsan is efficacious whenever it is given; but, it has been suggested that the best time for administering it is just before a relapse and as early in the infection as possible. The drug is best given intravenously in doses of 0.2 to 0.25 gm. to persons of average weight; it is efficacious, though much

less satisfactory, if given subcutaneously, and it has been given by the rectum in children. The spirochetes disappear and the temperature falls within twelve hours after the drug is injected. Ill effects, such as vomiting and a rise in temperature, may follow; they may be due to the sudden destruction of large numbers of spirochetes. Relapses after treatment occur in a small proportion (9 per cent.) but recovery is usually uninterrupted and strength and a normal blood count are quickly regained. If a relapse does occur a dose of 0.15 gm. of salvarsan controls it. Neosalvarsan is probably just as efficient and a much safer remedy than salvarsan, though its action may be rather slower. Atoxyl and tartar emetic, valuable in the treatment of trypanosomiasis, have little or no effect on relapsing fever.

The way in which the drug acts on the spirochetes is uncertain; but it is suggested, since the granular débris of destroyed spirochetes is found in the liver and spleen cells of cured animals, that the organism may play an important part in the destruction of spirochetes.

CHAPTER XVIII

YELLOW FEVER

By the late JAMES CARROLL, M.D.

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Definition.—An acute, specific, infectious disease, characterized by fever occurring occasionally in one, but generally in two, paroxysms; the first of these is of short duration and followed by a brief remission or intermission which is succeeded in turn by secondary fever, accompanied by albuminuria, jaundice, passive hemorrhages from the mucous membranes, and, in severe cases, black vomit.

Etiology.—From the time of Benjamin Rush the transmission of yellow fever through the atmosphere had been taught and believed; but such declarations were met with seeming proofs of its transmission by indirect contact, and by some it was held to be even directly contagious. English and Spanish physicians who had passed through large epidemics were about equally divided in opinion upon the subject. No matter to which side of the argument an authority might lean, facts and evidence were always forthcoming to show that his theory did not explain all the conditions encountered. For instance, persons who secluded themselves during an epidemic frequently became infected, while, on the other hand, many who were in constant attendance upon the sick escaped infection; and again, a single visit to the sick, and only one visit, was in many instances sufficient to insure an attack. The fact that certain buildings or localities, and vessels in particular, retained the infection during the warm season or in tropical regions, and the constancy with which the infection appeared to cling to the vicinity of water, led to the belief, and with reason, that it resulted from fermentation, the most favorable conditions for which require heat and moisture. The beginning of many epidemics could be traced to the presence of vessels recently arrived from the tropics, and as the holds of wooden vessels were nearly always in an offensive condition, the fermentation theory received strong support. After the discovery of bacteria there seemed to be no longer any room for doubt. It was very difficult to explain why persons suffering with the disease often failed to communicate it to others after having been removed only short distances.

It was shown that persons who contracted yellow fever on shore might be treated at a sufficient distance from the shore, on board vessels, without danger of communicating the disease to other persons on the same vessel. On the other hand, it was also well known that vessels frequently became infected while lying at ports where the disease prevailed; and these facts were hard to reconcile.

The first announcement of the discovery of a bacterium as the cause

of yellow fever was made by Domingos Freire, of Rio de Janeiro, who, in 1883, described his *Cryptococcus zanthogenicus* and claimed that it was the specific cause of the disease. Carmonary Valle of Mexico, Charles Finlay of Havana, and Gibier of Paris, each thought that he had discovered the specific cause of the disease; but subsequent investigations by Sternberg showed that they had been mistaken. Guiseppe Sanarelli announced in 1897 that he had cultivated the causative agent, and that by inoculations with it and with its filtered products he had produced the characteristic lesions of the disease in lower animals and the clinical phenomena in men. He named the organism that he had found *Bacillus icteroides*. Sternberg obtained a bacillus by the use of the ordinary culture media, and found that it proved to be pathogenic for lower animals. Because of his inability to establish its identity, he named it *Bacillus X*, and caused it to be preserved. Upon the publication of Sanarelli's results, Sternberg directed the late Major Walter Reed and the writer to undertake experimental work with *Bacillus X*, and later with *Bacillus icteroides*, for the purpose of comparison and identification. After working for several years it was concluded[1] that *Bacillus X* belonged to the colon group and *Bacillus icteroides* to the hog-cholera group and that the blood of yellow fever patients exerted practically no agglutinative effect upon *Bacillus icteroides*. Although persistent efforts were made to sustain the claim of Sanarelli for *Bacillus icteroides*, the best European and American authorities upheld the finding of the American Army Commission, that it was a secondary invader only.

In the year 1900, during the American occupation of Cuba, a commission composed of Drs. Walter Reed, James Carroll, Aristides Agramonte, and Jesse W. Lazear, of the United States Army, was formed on the Island of Cuba to investigate yellow fever. In a report published in October, 1900, they stated that they had been unable to find *Bacillus icteroides* in 29 cases, that *Bacillus icteroides* was not the cause of yellow fever, and that the mosquito served as the intermediary host for the parasite of the disease. After abandoning the search for *Bacillus icteroides* they decided to put the mosquito theory to the test, and for this purpose secured a number of volunteer subjects, among them two members of the commission, a contract surgeon named Pinto, and later, for other experiments, some soldiers and Spanish immigrants. Finlay had claimed to have produced yellow fever with mosquitoes kept from two to six days after biting a patient, and the mosquito suggested by him was the one used in making the tests.[2] Experiments were begun by Dr. Lazear in

[1] Reed and Carroll: *Jour. Exper. Med.*, 1900, vol. 5, No. 3.

[2] Dr. Charles Finlay (*Anales de la Academia de Ciencias Medicas de la Habana*, Habana, 1890–91, **27**, 501), of Havana, was the first to propound clearly a mosquito theory of the transmission of yellow fever, though an insect theory, which was made to include the mosquito especially, as well as certain other insects, was advanced by Nott, of Mobile, Alabama, in 1847. In 1876, Dowell, of Galveston, Texas, again called attention to the fact that the gnat and mosquito were governed by the same natural laws as yellow fever. A number of observers had previously noted the unusual prevalence of mosquitoes during epidemics. Finlay attempted to prove his theory, but could not have succeeded because his mosquitoes were kept only two to five days (in one case six days) after biting a patient. The cases among his subjects were clearly the result of the great prevalence of the disease in Havana at the time, and his tests lacked the precautions necessary to guard against accidental infection.

August, 1900, with mosquitoes kept from two to thirteen days after contamination, applying them to 9 individuals, without success; but in the 2 last cases, using the same mosquito kept twelve and sixteen days, respectively, the attempts were successful.[1] In September, Jesse W. Lazear, a member of the commission, knowingly permitted himself to be bitten by a stray insect in a yellow fever hospital while he was applying other mosquitoes to patients. He was bitten on September 13th, sickened on the 18th, and died on the 25th, after he had succeeded in showing in two other persons that the mosquito could convey the infection. He obtained immediate confirmation of his first case by applying the same mosquito at once to a second individual, on the day that the writer was taken ill. This second case also proved positive within five days after inoculation.

In order to further confirm and perfect the results obtained by Lazear, an isolation camp was established in which were placed two physicians, one an immune, the other a non-immune, with a number of soldiers and some Spanish immigrants, all of whom had expressed their willingness to submit to the experiments, and after a sufficient period of strict quarantine the following confirmatory tests were made: (1) Fifteen mosquitoes that had previously bitten patients with yellow fever were liberated in a mosquito-proof building especially constructed, and which had been divided by a wire-screen partition, extending from floor to ceiling, into two compartments, each of which was furnished with a bed that had been previously disinfected. The mosquitoes were liberated into one compartment and this was entered soon after by a non-immune, who, lying down upon the bed and exposing his chest and limbs, was bitten by several of the insects. He returned again for a short time on the same day, when he was again bitten by some of the insects, and on the following morning several more attacked him when he entered the third time for only a few minutes. This man became ill with a typical attack of yellow fever on the fifth day after he first exposed himself to the mosquitoes. On the evening of the day that this subject first entered the mosquito compartment, two other non-immunes were admitted to the opposite section, where they slept for eighteen consecutive nights, separated from the mosquitoes only by the wire screen partition. Their health was not disturbed in the slightest degree.

2. Another mosquito-proof house was constructed and supplied with several boxes of soiled articles of bedding and clothing direct from a yellow fever hospital. These articles had been intentionally soiled with urine, fecal matter, and black vomit from fatal and other cases of yellow fever. This house was entered for twenty-one consecutive nights by two soldiers and a contract surgeon, non-immunes, who, after unpacking the boxes, handled and shook the soiled articles, hung them upon the walls, and then retired for the might. In the morning they handled the garments again, and replaced them in the boxes. This was continued daily; the individuals remained in strict quarantine and were confined to the camp,

[1] "The Etiology of Yellow Fever—A Preliminary Note," by Reed, Carroll, Agramonte, and Lazear. Proceedings of the American Public Health Association at the 28th Annual Meeting, Indianapolis, Ind., October, 1900.

but spent the day-time in a tent set apart for the purpose, every night during the experiment being passed within the house and in the manner mentioned. At the end of three weeks another party consisting of two non-immunes occupied the house in the same way, with a fresh supply of contaminated articles from the hospital. They repeated the unpacking, handling, and repacking the soiled articles for twenty-one nights and none were infected. Newly soiled articles of bedding and clothing had been added from time to time, and after the receipt of another supply upon their release, two additional non-immunes slept in the house for twenty-one nights longer. These men passed their nights within the identical garments and between the same sheets that had been used by patients dying of yellow fever. One slept with his head upon a towel soiled with blood drawn from a patient in the first day of the disease, and which was shown by inoculation to be capable of infecting. These men also came out of the experiment building in perfect health, and had increased in weight. The majority of the men thus exposed were afterward inoculated by means of mosquitoes or by blood injections, and their susceptibility was proved by their becoming infected. This was deemed sufficient to show that susceptible persons might live and sleep in intimate contact with fomites from yellow fever patients and suffer no harm as long as they were not bitten by contaminated mosquitoes.

3. Men were singled out in certain tents within the camp, and contaminated mosquitoes, that had been kept sufficiently long, were applied to them, with the result that many contracted the disease. In every case the attacks followed within the usual period of incubation, and no other persons in the camp became infected than those purposely inoculated. Every precaution was taken, a strict quarantine was maintained, and the residents of the camp were required to sleep always beneath mosquito netting. It was shown by these experiments that mosquitoes were capable of communicating the infection as long as fifty-seven days after they had bitten a patient suffering with yellow fever.

4. It was further demonstrated that the subcutaneous injection into a non-immune of 2 cc., 1.5 cc., 1 cc., or 0.5 cc., of blood drawn directly from the vein of a yellow fever patient in the first or second day of the disease would cause an attack of yellow fever.

Twelve attempts at inoculation with mosquitoes kept from four to eighteen days after biting a patient all resulted in failure; but the insects used for these tests had been kept at room temperature during the months of November and December. In January there was another failure resulting from the application of twelve mosquitoes kept for twenty-two days at a temperature of 82° F. after they had bitten a very mild case in the eighth hour of the attack. Ten persons in all were infected by the application of mosquitoes during the winter, and the experiments showed conclusively that fomites cannot transmit the disease; that yellow fever can be communicated by blood injections; that an infected house is one that contains "ripe" infected mosquitoes; and that the mosquito is harmless until twelve days or longer after it has bitten a patient, but that it retains the power to infect as long as it lives.

The first to confirm the efficiency of the mosquito as the transmitting

agent of yellow fever was John Guiteras, of Havana, who, in the spring of 1901, infected a non-immune Spaniard by applying to him a contaminated mosquito. In August, 1901, Guiteras succeeded in producing 7 additional cases, and immediately after this it was demonstrated by a member of the Army Board (Carroll) that the diluted blood serum from a patient with yellow fever is capable of conveying the disease when injected subcutaneously in quantities of 1.5 cc. after having been passed through a new, sterilized Berkefeld filter. It was further shown that the blood of a patient could be deprived of its power to infect upon subcutaneous inoculation by subjecting it to a temperature of 55° C. for ten minutes.[1] In this work 6 additional experimental cases were produced, and all recovered, a total of 22 cases intentionally inoculated with yellow fever by the Army Board, without a death.

The doctrine of the transmission of yellow fever by the mosquito is firmly established. Marchoux, Salimbeni and Simond, the members of the French Commission, concluded that yellow fever is contracted in no other way than through the bite of the mosquito *Stegomyia fasciata;* that to become capable of infecting, the mosquito must bite a patient during the first three days of the disease, and that the mosquito is harmless until at least twelve days after biting a patient; that no other mosquito aids in the transmission of yellow fever; that simple contact with the patient, his garments, or excreta, will not communicate the disease; that yellow fever can become epidemic only in places where the mosquito exists; and that prophylaxis against yellow fever rests entirely upon the means taken to prevent mosquitoes from biting the sick and the well.

In New Orleans during 1905 with an epidemic beginning earlier in the season than usual, with a larger non-immune population than ever before, and with the disease well established early in August, great success was attained in controlling and stamping out the epidemic before its disappearance could be attributed to the occurrence of frosts. Could the permanent endemic foci be once destroyed, the United States and Mexico would be freed from yellow fever, and concerted action by the countries concerned would make it an easy matter to insure the permanent suppression of the disease.

The causal organism, a spirochæte, was discovered by Noguchi and termed *Leptospira icteroides.* This organism has been found in epidemics in various countries. A positive Pfeiffer reaction is given with the blood from convalescents. A disease with features similar to yellow fever in humans has been produced in animals.

Susceptibility.—All races are not equally susceptible; the white races, and especially those with fair skins and who inhabit northern climes, appear to suffer most. The negro is susceptible but not in the same degree as members of the white races. One attack of the disease generally confers permanent immunity and second attacks are rare. It is possible that a person after recovering from a very mild attack might become susceptible after a lapse of time. The incidence is greatest in young adult life, and the mortality rate is higher among those who are

[1] This experiment was repeated at Rio de Janeiro by the French Commission, who reduced the time of exposure at the same temperature to five minutes.

debilitated. The immunity enjoyed by the inhabitants of countries where the disease is endemic probably results from mild infections during infancy and childhood.

Pathology.—Yellow fever is a general infection with severe intoxication. The most marked effect of the toxin is seen in the liver, the probable reason being that the toxin possesses a marked affinity for the hepatic cells. From the clinical manifestations we would infer also that there is some affinity between the toxin and the cells of the central nervous system and perhaps those of the muscular system, as well as the vascular endothelium. The lesions in the digestive tract are chiefly mechanical and secondary to those in the liver; it is difficult to say to what extent the lesions in the kidney are due to the toxin and how much to secondary intoxication resulting from damage to the liver.

Rigor mortis appears early and is very marked. When death takes place on the eighth or ninth day, the skin of the trunk is usually of a canary-yellow color. This is less intense on the extremities, but the eyeballs are deeply tinted and the face is distinctly yellow. The intensity of the color varies usually with the stage and severity of the attack. The dependent parts of the body are deeply discolored and livid, and the same is true of the tips of the fingers and toes, scrotum, penis, etc. Hemorrhages beneath any or all of the serous membranes are frequent. No constant lesions are found in the brain and spinal cord. The vessels are usually engorged, and hemorrhages frequently take place into the brain substance and beneath the membranes.

The lungs are the seat of marked hypostatic congestion, with hemorrhage; and hemorrhages are often visible beneath the pleural membrane. The heart is distended; its muscular tissue is of a deep reddish-brown color and sometimes softened in consistency, but this is not constant.

Digestive Tract.—The stomach may be found distended with black, fluid blood, even in cases in which black vomit did not appear during life. After removing and washing the stomach, its mucous membrane may be found pale and eroded, or blood stained. At the pyloric end there is congestion of its mucosa, as a rule, and there may also be found large areas of diffused submucous hemorrhage.

The mucous membrane of the duodenum is always deeply congested, swollen, and the seat of hemorrhages. The condition of the jejunum and ileum depends upon the duration and severity of the attack. The upper part of the jejunum is usually involved with the duodenum, and the congestion may continue for some distance into the ileum. On the other hand, the ileum may appear practically free from any pathological lesion after the contained blood has been removed. The passive congestion in the mesentery and intestine, which results from compression of the capillaries by the swollen liver cells, is manifested earliest and with the greatest intensity in the pylorus and duodenum. Passive congestion is always more marked in this region (duodenum) than lower down, and invariably accompanies the disease. This is probably the explanation of the tenderness on deep pressure in the epigastrium.

The *liver* is tense, firm, and smooth; the color is variable. It may be uniform or mottled but is always yellowish or brownish and usually

shows areas of congestion or hemorrhages beneath the capsule. Upon section the organ is firm, pale, and friable. The liver cells show marked variations in size and their normal outlines are distorted. The majority are densely packed with medium-sized fat droplets, and the protoplasm of some is coarsely granular. The degree of fatty degeneration is variable, but it is always present in remarkable degree; in certain instances practically all the lobules are affected throughout while in others whole lobules or small areas may escape. The jaundice results from the pressure of the swollen liver cells upon the smaller biliary vessels.

In the excessively degenerated condition of the liver in the advanced stages of severe attacks but little urea can be formed, and the carbonate, carbamate, and lactate of ammonium, being no longer converted by the liver into urea, are retained in the circulation. Urea is deficient in the urine in yellow fever because the liver no longer provides the normal quantity. The delirium and coma (with or without convulsions) in fatal cases are due to ammonemia and not to uremia, and by the early elimination of toxin we lessen the degree of fatty degeneration of the liver and diminish the tendency to anuria, to severe intestinal hemorrhages, and to the ammonemic intoxication superadded in the fatal cases.

Kidneys.—The condition of the kidneys is more variable than that of the liver because involvement of these organs is not so general or so intense. In the fresh condition the kidney is of normal size or slightly swollen, pale, and fatty, or congested. Acute diffuse nephritis is usually found; the lesion is sometimes of a distinctly degenerative type; in others it consists of not much more than well-marked cloudy swelling. The glomeruli may be swollen and engorged or atrophied; the capsular epithelium may have suffered but little change, or it may have become swollen or degenerated, or have entirely disappeared.

Spleen.—The spleen may or may not be enlarged and soft, but it is always congested. The swelling, when present, is probably due to the presence of bacteria as secondary invaders.

The old idea that the blood undergoes degenerative changes in yellow fever is without foundation. In the later stages many of the leukocytes may contain minute fat droplets or vacuoles, and there may be some anemia; but in the early stage there is no marked anemia, no cell destruction, and the leukocytes are practically normal in number and appearance. In a small proportion of the cases a moderate degree of polymorphonuclear leukocytosis can be demonstrated.

Symptoms.—The earliest symptoms may be a premonitory feel ng of malaise, with pain in the back and loins, or a slight frontal headache. There is usually a furred tongue, with constipation. In the majority no marked premonitory symptoms are noted.

At the *onset* there may be a sudden chill. The patient may have lost his appetite and have gone to bed to rest and sleep in the middle of the day, to wake with high fever. With the onset of fever there is a sharp headache, generally frontal, but occasionally occipital in location; the face is flushed, the eyes injected, rachialgia is often present, and the temperature may range anywhere from 102° to 106° F. or even higher. In mild cases the skin is moist; in severe ones dry and hot; constipation is

usually present; the tongue is clean or lightly coated and its tip and edges red; photophobia may be pronounced or absent; the pains may be agonizingly severe or very mild in character; nausea may be absent, but usually it is present and followed by vomiting of a clear colorless or yellowish or greenish fluid. The symptoms are all more or less pronounced, depending upon the character of the attack. There may be great epigastric distress and the amount of urine may be small, but no albumin is found. At this stage the case resembles one of any severe infection. On the second day the temperature may remain elevated or a fall may be observed; the headache and body pains may have abated or they may continue; the photophobia is more marked; the flushing of the face and ocular injection are pronounced; a slight yellowish tinge of the eyeballs can be distinguished. The stomach may be quiet, or the nausea and vomiting may be distressing but somewhat abated. There may be suppression or retention of urine. The skin of the chest is of a dusky hue, and upon pressure it is seen that the capillary circulation is sluggish. On the third day the temperature may remain about the same or fall several degrees and then rise to near its original height, or it may fall gradually and decline during several days by lysis. A sudden drop in temperature to subnormal, with the appearance of black vomit and suppression of urine at this time, almost certainly means a fatal issue. More frequently, after a brief decline on the second day, the temperature rises gradually to 103° or 104° F. and remains there with a morning fall of 1° or 2° for one, two, or three days, and then declines gradually to normal. Vomiting may return and the material ejected may contain fly-wing specks or coffee-ground granules, or it may consist of the brownish or brownish-black fluid known as black vomit. The jaundice is now (fifth or sixth day) quite intense, great weakness and prostration are manifested; there may be cramping pains in the abdomen, with the passage of a large amount of tarry material; these may be accompanied or followed by persistent hiccough, delirium, convulsions, coma, and death. The remission or intermission in temperature may occur after twenty-four, forty-eight, or seventy-two hours.

Faget's Sign.—Following the remission or intermission, a singular and progressive diminution occurs in the pulse-rate, so that with the secondary exacerbation of fever there is the anomaly of an ascending temperature with a slowing pulse, and this continues regardless of the temperature. With the appearance of jaundice, at this time, the pulse-rate diminishes to 70, 60 or even 50 per minute. In well-marked cases this is a valuable and fairly constant sign, but in the milder cases the lack of correlation between pulse and temperature is less apparent.

Epistaxis may be present early, but a more reliable sign is the condition of the gums. At the beginning of the fever they may be swollen and spongy; a day or two later a red line is seen at the margins and upon gentle pressure blood can be made to exude. In severe cases the oozing may be constant and sufficient to stain the lips and tongue. As the disease progresses the tongue becomes, at first lightly, then heavily, coated, and later it may become fissured and bleeding so that the saliva, lips, and tongue, are all blood-stained. Hemorrhages from the mucous

membrane of the mouth, nose, intestine, and genito-urinary tract (especially in females) are frequent after the fifth or sixth day.

Skin.—The skin of the face and chest may bear a blotchy or clean petechial eruption in mild as well as in severe cases, and the appearance may resemble that of a mild eruptive fever. Small macules, papules, pustules, or blebs, may appear after the disease has developed. If these become hemorrhagic the outlook is serious.

Urine.—A trace of albumin is found on the second or third day, and the amount may increase rapidly until the specimen coagulates upon being heated. The albumin usually disappears from the urine with defervescence, but albumin or casts may persist for several months after severe attacks. After a day or two hyaline and finely granular casts appear, and on the fifth or sixth days there are coarsely granular and epithelial casts, which show a more or less deep staining with bile pigment. Red blood cells may be present at about this time and may be scarce or abundant according to the tendency to hemorrhage. The intensely dark color of the urine, about the sixth or seventh day, is due to the presence of bile, though it is not rare to find blood present.

Mortality.—Under favorable conditions the mortality should not exceed 10 or 15 per cent.; it should never exceed 20 or 25 per cent. under any circumstances, and a higher death-rate would warrant the suspicion that the milder cases were escaping recognition. A fairly large proportion of cases of yellow fever are mild in character and recover without black vomit.

Sequelæ.—But few sequelæ follow yellow fever. Recovery takes place quickly, as a rule, and the patient rapidly regains weight and strength. In a small number recovery is followed by a period of weakness and debility which may persist for one or two months. Suppurative inflammation of the parotid and other glands, abscesses, and furuncles, are the only sequelæ that deserve mention, and these yield slowly to the ordinary measures as the patient's strength and vitality improve.

Diagnosis.—The period of incubation being from two to six days, usually from three to five, will aid in determining the probability of exposure in persons who present suspicious symptoms in places removed from the habitat of the disease. The early suffusion of the face and eyeballs, vertigo, frontal headache, pain in the lumbar region and loins, pains in the extremities (chiefly the lower ones, but not involving the joints), nausea and vomiting, with ocular jaundice on the second day, should excite strong and suspicion; and with the accompanying tenderness elicited by deep and gentle pressure in the epigastrium the diagnosis would be reasonably certain. The chill or rigor may be absent, the headache may be occipital, vomiting may not occur, and the temperature may not rise above 102° F. in a mild case. Malaria and most inflammatory conditions can be excluded by examination of the blood. In relapsing fever spirochetes will be present in the blood during the febrile exacerbation; in typhoid fever the bacilli may be obtained in blood cultures; and in these infections albumin is not as likely to be present in the urine on the second day as in yellow fever. Mild cases may be extremely difficult of diagnosis, but the knowledge of exposure and the

symptom-complex, as a whole, with ocular jaundice on the second day, together with marked epigastric tenderness, would justify a provisional diagnosis of yellow fever in the absence of special contraindications. Faget's sign, albuminuria, bloody oozing from the gums on pressure, and fly-wing material in the vomitus, render the diagnosis complete. In the severer cases the diagnosis becomes clear by the third day at the latest.

A sudden fall in the temperature to subnormal in the first few days, suppression of urine, hiccough, black vomit, and free intestinal hemorrhages, are all indicative of grave attacks.

Guiteras called attention to some aids in diagnosis. He believes that Ehrlich's diazo reaction is practically never present in uncomplicated cases of yellow fever, although it may be present in severe cases of dengue. He has been able successfully to exclude yellow fever by obtaining the Ehrlich diazo reaction in the urine.

A point of importance in the differential diagnosis between dengue and yellow fever brought out by Van der Berg, is that in dengue there is a leukopenia, the leukocytes being reduced on the average about one-half. Stitt confirms the statement in regard to dengue, in which he found a polymorphonuclear as well as a general leukopenia, with a marked relative increase of the mononuclear leukocytes. This is in marked contrast to the condition of the blood in the early stage of yellow fever, in which the total leukocyte count is practically normal and there is no diminution in the proportion of polymorphonuclear leukocytes; on the contrary they are frequently increased.

Prognosis.—In every case, no matter how mild, this must be guarded. Even in those which are apparently trivial, grave symptoms may develop after errors in diet, permitting the patient to leave his bed, or failure to maintain the eliminative functions. A quiet stomach, low temperature, soft skin, the ability to sleep, and a free flow of urine, are all favorable. High temperature without remission, intense and persistent headache, nausea, and nervous irritability, indicate a more serious condition; a temperature above 105° F., delirium, singultus, black vomit, partial suppression of urine, convulsions, dark petechial spots, and hemorrhages into the skin or intestine, are of grave significance. Complete anuria, free intestinal hemorrhages, profuse black vomiting, with hiccough and coma, are of fatal import.

Treatment.—**Hygienic and Prophylactic.**—The most important duty of the physician during an epidemic, or in the possibility of an epidemic of yellow fever, is to institute preventive measures to guard against extension through the agency of the mosquito, and it is necessary to see that proper precautions are taken by non-immunes to exclude the chances of being bitten by mosquitoes that are possibly infected. *Stegomyia fasciata* is a twilight mosquito that feeds, as a rule, early in the morning and in the afternoon until 10 o'clock at night. It usually rests in the middle of the day and non-immunes may visit well-lighted places in infected localities between 9 A.M. and 3 P.M. with almost absolute impunity. But at 3 P.M. the danger begins, and after this hour one should go to high localities without the infected city, or retire within a building thor-

oughly protected by wire screens. Every measure should be used to reduce the number of mosquitoes. All persons in an infected locality suffering from fever of unknown origin, particularly if it begins with a chill and headache, should be isolated at once and placed behind mosquito-proof wire screens and mosquito netting. These precautions should be continued until the temperature remains normal. As soon as a patient suffering with yellow fever is removed from a room, it should be tightly sealed and fumigated with pyrethrum, using at least one-fourth pound to each 1000 cubic feet. After five or six hours the stupefied insects should be swept up from the floor and burned. Tobacco and sulphur are more efficient but more disagreeable than pyrethrum.

Disinfection of the person, effects and surroundings of a patient is useless. A quarantine period of at least five days is necessary, and measures should be taken to protect ships against mosquitoes when lying at infected ports. One-fourth of a mile is a safe distance from shore, and the proximity of other vessels should be avoided.

As a matter of personal prophylaxis non-immunes should never spend the night in an infected locality. Should exposure after dark in such localities be unavoidable, then mosquito headnets, gauntlets, and leggings should be worn, and upon retiring the person should see that mosquitoes are expelled from the room or destroyed by fumigation. The sleeping-room selected must be as high as possible above the ground; the bed and its vicinity must be free from mosquitoes and perfectly protected by intact netting of 1.0 or 1.5 mm. mesh. It is unsafe to rely upon the use of the essential oils, spirit of camphor, etc., upon the skin.

In the matter of general prophylaxis it is necessary to bear in mind that three factors are indispensable for the production of an outbreak, *viz:* (*a*) preëxisting cases of the disease; (*b*) mosquitoes of the genus *stegomyia;* and (*c*) the presence of non-immunes. In the absence of any one an epidemic is impossible. The most rational and effective procedure is to prevent the interaction of *a* with *b*; if this be effected, *c* may be disregarded. Failing to prevent the contact of *a* with *b*, then if *b* and *c* be permitted to come together after the proper interval, infection results, and can be brought about in no other way, without experimental inoculation.

An interval of about two or three weeks *must* elapse after the importation of the first case before the appearance of secondary cases, and whenever the course of an outbreak is being traced in other than an epidemic locality, it can be safely taken for granted that whenever a group of cases is found to occur together the primary case from which the group originated must have existed two or more weeks earlier. If instead of a group only a single secondary case is produced, the difficulty will be very great, because it may be assumed that this is the primary case. Two weeks, represents the shortest known developmental or incubative period (twelve days) in the mosquito, plus a short period of incubation in the human being.

Good results are claimed in prevention both from the use of serum and vaccine. The latter appears to have reduced the case incidence in epidemics if given sufficiently in advance of exposure (ten to fifteen days). It seems to protect for five or six months.

Medical.—This is in a sense prophylactic, because by putting the patient to bed early and instituting proper treatment we can lessen the severity of the attack, and in some cases avert a fatal issue.

It is of vital importance that the patient be put to bed and kept perfectly quiet upon the manifestation of the earliest symptoms. The bowels should be moved by a mild cathartic. Usually sulphate of soda is the best, in doses of 4.0 gm. (1 dram) every hour, until the desired result be obtained, or six doses have been given. If the bowels fail, to respond within an hour after the sixth dose, an enema of soap and water should be given. The saline may be preceded by a small dose of calomel with bicarbonate of soda, 0.23 gm. (3 gr.) of each. Following the catharsis a hot mustard foot-bath should be administered, and the patient then be covered with blankets to induce free perspiration. Hot lemonade may be given to aid diaphoresis. If the irritability of the stomach is not relieved mustard should be applied locally, and iced carbonated Vichy water in small quantities, or small doses of sodium bicarbonate, 0.2 gm. (3 gr.), in cold mineral water, administered. All food must be withheld during the first three or four days, and the patient should be encouraged to drink carbonated Vichy water freely and often, and always ice cold. If this is not at hand any of the alkaline mineral waters may be substituted, after adding about 2.0 gm. (30 gr.) of sodium bicarbonate to the pint. The effervescing mixture of Anderson serves an excellent purpose; he adds 30 gr. of potassium bicarbonate to a dessertspoonful of fresh lime juice and gives it every two hours while effervescing. He is particular to state that it must be neither alkaline nor acid but neutral. Both Touatre and Anderson state that since their adoption of the Vichy water and effervescing mixture, respectively, they have ceased to see the profuse black vomit and hemorrhages formerly observed. For the cephalalgia ice-cold applications are best; the pain passes off after a few hours—twenty-four at most. The coal-tar preparations and morphine should be avoided as a rule.

With high fever cold sponging should be done every hour; or the wet pack or bath may be used. In the beginning, if the skin be dry and pungent, sweet spirit of nitre, in doses of 2.0 to 4.0 cc. ($\frac{1}{2}$ to 1 dram) in a little iced water every half or every hour until the skin become moist, may be given. The patient should be encouraged to drink alkaline waters freely, and if there be persistent nausea or irritability of the stomach, alkaline fluids should be given cold by rectal injection.

Food being withheld for the first three or four days, the patient should be supplied freely with fluids. It is now thoroughly established that sodium bicarbonate exerts a markedly beneficial effect; whether it is because it remedies a deficiency of alkali or neutralizes an acid poison remains to be shown. After the third or fourth day, if the temperature continues below 101° F. and the patient craves food, he may be given a tablespoonful each of milk and lime-water, cold toast-water, or barley-water, in small quantities and at rather long intervals at first, until the effect has been noted. Pure frozen cream and gelatine in the form of wine or lemon jelly are beneficial, and may be given in small quantities if they are enjoyed. After three days of normal temperature, if the patient's

condition be good, he may be given milk, chicken broth, blanc mange, ice-cream, or custard, and fresh juicy fruits, followed by soft-boiled eggs, toast, etc.

Alcohol, best in the form of champagne, tends to allay nausea and vomiting and is mildly diuretic. It should be given in doses of about 15 cc. (a tablespoonful) with ice, every two, three, or four hours, as indicated by the condition of the patient and its effect. It should be given on the second and third days of the fever only when the effect is beneficial. The stronger forms of alcohol are not so desirable, but they may be used cautiously with persons who are accustomed to and prefer them. They should be well diluted.

If at the outset we preserve the integrity of the vascular endothelium, keep the blood moving within the capillaries, and secure elimination of the maximum amount of toxin, then, if the heart, liver, and kidneys were previously sound, we prevent the occurrence of excessive hemorrhages, and the patient's recovery is practically assured.

It is necessary to record the amount of urine. Retention and suppression are frequent, the latter occurring late and the former early. Every specimen passed should be measured and tested for the presence of albumin, because its early appearance in large quantity is an indication of a severe attack. However large the quantity of albumin the physician may feel encouraged if the patient pass from 500 to 1000 cc. of urine in twenty-four hours. Free elimination early in the attack lessens the tendency to hemorrhage and modifies the subsequent course. Hence the great importance of instituting eliminative treatment at the earliest moment, and as all toxins are removed chiefly by the kidneys, it is essential to secure early and free secretion by these organs. If black vomit or intestinal hemorrhages occur oil of turpentine in 0.6 cc. (10 minim) doses deserves a trial, with application of ice to the epigastrium, and alkaline waters by the mouth or rectum.

The patient should not be permitted to sit up or leave his bed until after several days of normal temperature.

CHAPTER XIX.

SPIROCHÆTOSIS ICTERO-HEMORRHAGICA. RAT-BITE DISEASE.

By ELMER H. FUNK, M.D.

SPIROCHÆTOSIS ICTERO-HÆMORRHAGICA.

Synonym.[1]—Spirochetal Jaundice.

Definition.—An acute infectious disease caused by the *Leptospira ictero-hæmorrhagiæ*, commonly found in rats which act as the source of infection for man, and characterized clinically by fever, jaundice, enlargement of the liver, and a tendency to hemorrhages.

It is especially prevalent in Japan, but cases have been reported from Africa, the various European countries, Peru, Brazil, and the United States. It may be said to occur endemically in Japan and Egypt, epidemically in various parts of the world, and sporadically anywhere.

Etiology.—The *Leptospira ictero-hæmorrhagiæ* was described in 1914 by a group of Japanese investigators[2]. The spirochete commonly infects rats in various parts of the world and it is believed that man is infected through contamination of the soil and water by the urine of infected rodents and those ill with the disease. The spirochetes enter through the skin or by mouth. Farmers and miners are predisposed. In Japan the disease occurs in wet mines and disappears when the mines are pumped dry. During the World War the disease was endemic in rat-infected wet trenches. The spirochetes invade the blood stream early in the disease but disappear by the fifth or sixth day. They are found in the urine toward the end of the second week and may persist for months. They may also be found in the cerebrospinal fluid and in bloody sputum. Their presence can be demonstrated by dark-field illumination, various staining methods, and by intraperitoneal inoculation of guinea-pigs. The inoculated animals develop jaundice, hemorrhages, and albuminuria; and from these animals the spirochete is readily recovered. Noguchi has cultivated the spirochete on special media.

Pathology.—The liver is enlarged and shows evidences of granular and fatty degeneration. There is not, as a rule, the picture of acute yellow atrophy. The spleen is soft and slightly, if at all enlarged. Duodenitis may be present and intense. Hemorrhage may be present in the gastric and intestinal mucosa. The kidneys show degenerative changes and in some cases hemorrhages. The spirochetes are found in the liver and kidneys.

Symptoms.—The period of incubation is from five to seven days. The onset is usually sudden with chills, headache, pain in the back and muscles,

[1] The term Weil's disease has been used as a synonym for this disease, but as it has been applied to different forms of jaundice it would be well to drop it from our terminology.

[2] Inada, Ido, Hoki, Kaneko, and Ito, *Jour. Exp. Med.* 1916, **23**, 377.

vomiting, diarrhœa, and prostration. The temperature rises abruptly to 102 to 104° F. and continues irregular for a varying period of ten to fourteen days, ending by lysis. In some cases the temperature drops by lysis on the fifth day, followed by a second rise, continuing for a week with gradual defervescence. The *jaundice* appears usually about the third or fourth day and reaches its height about the tenth or twelfth day. *Hemorrhages* are not uncommon in the severe cases and may occur from the mucous membranes or in the skin (purpura). Nasal and intestinal hemorrhages are common; gastric hemorrhage, hematuria, and hemoptysis occur less frequently. *Herpes*, which may be hemorrhagic, occurs in about 40 per cent. of the patients and later a macular or erythematous rash may appear. The liver is enlarged and tender. The spleen may or may not be felt. The superficial lymphatic glands are frequently palpable and tender. The urine is scanty, high colored, and contains albumin and bile pigment. The feces are usually light brown in color, but may be clay colored. Constipation is marked. The pulse, at first rapid, becomes slow with the advent of jaundice. The nervous symptoms may be quite marked. The early prostration is a striking feature. Sleeplessness, delirium, twitchings, convulsions, and coma, may occur in fatal cases. The blood examination reveals an increase in the coagulation time, a reduction in the hemoglobin, red cells, and platelets, and a polymorphonuclear leukocytosis (15,000).

The predominance of certain groups of symptoms has led some observers to describe renal, meningeal, typhoidal, and other forms of the disease.

Diagnosis.—This must be made from many other diseases associated with jaundice, more particularly yellow fever, malaria, relapsing fever, non-spirochetal infectious jaundice, etc. A careful study of the clinical picture and the various laboratory studies are conclusive. The dark-field examination of the blood early in the disease, and the urine later, may reveal the spirochetes. Intraperitoneal inoculation of guinea-pigs is valuable in demonstrating the spirochetes. The examination of the spinal fluid in the meningeal form may reveal large numbers of spirochetes.

A specific agglutination test, using cultures of the spirochete, or centrifulgalized urine containing these organisms, has been devised (Martin, Pettit, and Vaudremer). The test is said to be positive from the sixth to the tenth day and may persist for many months.

Prognosis.—The mortality varies from 5 to 30 per cent.

Prophylaxis.—This consists of sterilization of the urine and feces of patients and of measures directed toward exterminating rodents. Noguchi has prepared a vaccine for prophylactic inoculation.

Treatment.—This is largely symptomatic. Rest, a light diet, and the free administration of fluids are indicated. Fluids by bowel and nutrient enemata may be necessary if vomiting is present. Convalescent serum has been used. A polyvalent serum from horses injected with the spirochete is given intravenously in doses of 20 c.c. at intervals of several hours for at least four days (Manson-Bahr). In advanced cases with uremic symptoms the method is of little value (Manson-Bahr). Arsphenamine has no effect.

RAT-BITE DISEASE.

Synonyms.—Sodóku; Rat-bite Fever; Rattenbisskrankheit.

Definition.—An infectious disease, following rat-bite, characterized by recurrent paroxysms of fever, muscular pain, and erythema.

Distribution.—Sodóku is described in the earliest medical literature of Japan. It is endemic in the four chief islands, and, while not common, is more prevalent there than in any other country, so far as known. Owing to the frail construction of the houses, rats enter freely and sleeping persons are frequently bitten. Only a small percentage develop the rat-bite disease. The more recent Japanese observers conclude that diseased rats of both field and house species may convey the infection. Outside of Japan the disease has been reported from China, Australia, the Philippines, England, France, Italy, Germany, Spain, Morocco, Brazil, and the United States. The unity of the malady in the various lands is not fully established.

Etiology and Pathology.—Various organisms have been regarded as of etiological importance, such as a streptothrix, by Tileston, Schottmüller and Blake, a sporozoön by Ogata, and a diplococcus by Douglas, Colebrook, and Fleming. In 1915 Futaki and his associates in Japan described a spirochete, *Leptospira morsus muris*, in the swollen lymph glands of a rat-bite fever patient. Numerous Japanese observers have since found the spirochete in the blood, skin, lymph nodes, kidneys, and adrenals of patients with rat-bite fever.

It has been estimated that from 3 to 12 per cent. of the rats of Japan are infected. In infected animals (rats, mice, guinea-pigs) the *Leptospira morsus muris* is found in the blood during the first few weeks, later it becomes distributed in the connective tissues, especially of the bridge of the nose, lips, and tongue. A break in these tissues is the source of the spirochetes inoculated in the bite. They are not secreted in the saliva.

Persons of all ages and both sexes are affected. There is some evidence for individual variation in susceptibility. Many who are bitten by rats never develop the disease. Farmers, seamen, soldiers in the trenches and others whose occupations expose them to rat bites are especially predisposed. If the wound is in the exposed parts infection is more likely to occur. A mere scratch may be sufficient to cause infection.

Few necropsies have been done in human cases and these have not shown any significant changes apart from degenerative changes in the liver and kidneys. In the tissue at the site of the wound are lymphoid and connective tissue hyperplasia, hyaline degeneration and thickening of the bloodvessels.

Symptoms and Course. The bite wound usually heals spontaneously in a few days. After an incubation period of a few days to several months (average two weeks) there is a sudden onset with chill, fever, malaise, and sometimes joint pains. The temperature may reach 104° F., or higher. The fever persists for two to four days with remissions more or less marked, and falls suddenly to normal. During the febrile period there is headache, intense muscular pain, and often delirium. Coincident with the onset of the paroxysm, the bite wound becomes swollen,

bluish-red in color, and usually shows suppuration and necrosis later on. Reddish streaks appear in the direction of the local lymph nodes which become enlarged and tender. After sloughing, a circumscribed ulcer is left which heals rapidly.

The *erythema* is of the exudative type and appears in the first or later paroxysms and recurs with each exacerbation. The spots are seen on the extremities, face, and trunk, and vary from 0.5 to 5 cm. in diameter. They are slightly raised, bluish-red, and not tender to touch. They fade slowly with desquamation and leave a stain in the skin which persists for some time. In addition severe transient urticaria is common toward the end of the disease.

The apyrexia lasts three or four days to two weeks, when another paroxysm is ushered in with chill, fever, and a fresh crop of erythematous spots. As the disease progresses, the febrile paroxysms tend to grow shorter. The periodicity of the fever varies, but is fairly constant for the individual case. The respiratory and circulatory systems are but little affected. Appetite is poor and there is often diarrhœa in the more severe cases. The liver and spleen are never enlarged in uncomplicated cases. Only such lymphatics as drain the area of the bite wound become swollen. A transient or permanent nephritis may develop with the severe cases. The blood shows an eosinophilia and during the febrile paroxysm a leukocytosis of about 15,000 (Stitt).

The duration of the malady is a few weeks to many months, rarely a year or more. In addition to the classical type, there is an *afebrile* group with severe nervous symptoms, muscular palsies, coma, and death. An *abortive* type is also known, which ends favorably after one or two paroxysms.

Of the nervous features, delirium, coma, rarely twitching or convulsions, extensive paresis of the muscles of the extremities, anesthesia, and paresthetic skin areas may be found.

Diagnosis.—The cardinal features are: History of rat bite, relapsing fever, erythema of a bluish-red color, and muscular pain. The *Leptospira morsus muris* should be sought in the blood by dark-field illumination during the febrile attack. By inoculation in animals, preferably mice, the spirochetes can be demonstrated in from five to fourteen days. Malaria is differentiated by the blood picture and enlarged spleen. The differentiation from pyogenic infections, relapsing fever, trench fever, and syphilis should occasion no great difficulty.

Prognosis.—The severity of onset, preponderance of nervous symptoms, and length of febrile paroxysms are important in determining the outcome. Marked œdema is of the gravest significance. The mortality is estimated at 10 to 15 per cent.

Treatment.—Free excision of the wound, even several weeks after the bite, supportive diet, and symptomatic therapy are indicated. Good results have followed the use of arsphenamine. A course of six injections is usually sufficient to abolish completely all the symptoms and bring about a permanent cure (G. C. Low).

PART IV

DISEASES CAUSED BY ANIMAL PARASITES

By CHARLES WARDELL STILES, Ph.D., D.Sc.

GENERAL DISCUSSION

Nature and Kinds of Animal Parasites.—A parasite is an organism which lives in or upon another organism, called the host, and generally belonging to a widely distinct species, at whose expense it derives its nourishment and habitation. Thus the prime ideas in parasitism are food and association.

1. **Food.**—No distinct line can be drawn between a parasite and a predaceous animal, although, as a rule, the parasite attacks organisms which are larger, stronger, and more intelligent than itself, and does not immediately kill and devour its host, while the predaceous animal attacks animals which are smaller, weaker, and less intelligent than itself, and it kills and devours its prey.

2. **Association.**—This may present an instance of: (*a*) *Mutualism*, when the partnership results in benefit to both parties, as in the case of the sponge growing on the back of a crab; or (*b*) *Commensalism*, when the association results in a benefit to one party (the messmate), but neither benefit nor injury to the other (the host), as in the case of the non-pathogenic *Endamoeba coli* in man; or (*c*) *True parasitism*, when the association results in a benefit to the parasite, but an injury to the host, as in the pathogenic *Endamoeba histolytica*, or trichinæ, hookworms, or the tapeworms in man.

A parasite may visit its host only at intervals to take up temporary residence and to obtain food; such animals (mosquitoes, bed-bugs, etc.) are called *temporary* parasites. Others are more or less stationary with their hosts, and are therefore called *stationary* parasites; of these, we may have *periodical* parasites, which spend a given period of their life with their hosts (as bots under the skin, or *Strongyloides stercoralis* in the intestine of man), or we may have *permanent* parasites, such as trichinæ, in which the entire life-cycle is parasitic. Some parasites, as hookworms, require only one host to complete their life-cycle; others, such as the large tapeworms, require two or three hosts—an *intermediate host* in which the larval stage lives, and a *definite* or *final host* which harbors the sexual stage. All cases thus far cited are examples of *simple* parasitism, but we may have parasites which are parasitic in or upon other parasites, a phenomenon known as *hyperparasitism*.

We may further have *ectoparasites* (as lice) which live upon animals, and *endoparasites* (as tapeworms) which live in animals. The term *entozoa* refers primarily to the *endoparasites*, and *helminthes* refers especially to the parasitic worms, while *helminthology* is that part of zoölogy which deals with worms, especially the parasitic forms, and *helminthiasis* denotes an infection with parasitic worms.

Chance parasites, or *pseudoparasites*, are animals which are usually free-living but are, by chance, living as parasites (as the vinegar eel in the human bladder) or parasitic animals which by chance are not in their normal host (as *Fasciola hepatica* in man). *Spurious parasites* are objects which are described as parasites or mistaken for such, but which in reality are creations of the imagination (*Furia infernalis, Vermis umbilicalis*), or half-digested food (*Diacanthos polycephalus; Striatula;* banana cells mistaken for tapeworm segments, etc.)

Frequency.—As a general rule, the smaller a parasite is, the more individuals there may be in a patient; compare, for instance, *Taenia saginata, Ascaris lumbricoides, Enterobius vermicularis, Endamoeba coli, Giardia lamblia.*

There is no species of animal, and no race or class of man known to be free from parasites. We may lay down certain general rules covering the frequency of infection: (1) Certain parasites are more common among people of careless personal habits than among those of more careful personal habits; thus, as a rule, dwarf tapeworms, ascarids, and pinworms are more common in children than in adults, and whipworms are said to be more common in negroes than in whites. (2) Certain parasites (ascarids) are said to be more common among people who drink unfiltered water than in those who have a filtered water supply. The difference in frequency is influenced, however, by the disposal of feces by a better sewage system in cities than in villages. (3) Certain parasites (trichinæ, pork tapeworms) are likely to be more common among people who eat raw or rare pork than among people who eat their pork well cooked. (4) Certain parasites (hydatids) are more common among people who keep large numbers of dogs and live more intimately with them, than among people who keep fewer dogs in proportion to the population. (5) In general, animal parasitism increases from temperate to tropical climates. (6) All intestinal and some hepatic parasites decrease hand-in-hand with the increase of care exercised in a proper system of privies or sewers.

Age and Sex of Patient.—Some parasites (ascarids, pinworms) are more common among children, while other species (large tapeworms and hydatids) are more common among adults of from twenty to forty years of age; some parasites (large tapeworms, hydatids, head-lice) are more common among women than among men, while other species (lung-flukes, pubic lice) are more common among men.

Fertility of Parasites.—Most parasites are exceedingly fertile, some of them almost representing egg-machines. This fertility is:

1. A natural result of their environment, since they live in the midst of their food, provided by their hosts; hence energy which might otherwise be expended in seeking necessary food, may be turned to growth and

reproduction. It is estimated that the fat tapeworm (*Taenia saginata*) increases at the rate of thirteen segments per day, growing 3 cm. per day for the first month and averaging 14 cm. per day for the second month, and producing 150,000,000 eggs per year.

2. Subject to natural selection, for the life-cycles are often very complex, hence in such cases the chances that any one egg has of reaching sexual maturity are very small, so that individuals which are only slightly fertile would probably not be represented by many generations.

3. In accordance with the *general* biological law (not without exceptions) that the smaller an animal, the more fertile it is.

Resistance of Parasites.—Some parasites, especially in their egg and encysted stages, are exceedingly resistant to external influences: the Persian argas may live five years without food; *Cysticercus cellulosae* may live four weeks or so after its host is dead; trichinæ may live for months after their host (hog) is slaughtered; eggs with thick shells (ascarids, whipworms, *Taenia*) are more resistant than eggs with thin shells (hookworms, pinworms, dwarf tapeworms).

Seasonal Periodicity.—Some parasites show a decided seasonal periodicity: hookworms have a better chance to develop in warm, moist months than in cold or hot dry seasons; and in general this obtains for worms which do not require an intermediate host. For certain worms (as trematodes) which do require an intermediate host (as snails) the seasonal periodicity depends upon the seasonal activity of this host, and this activity may depend upon various factors, such as moisture and warmth.

Heredity of Parasites.—From the strict embryological point of view, it would be impossible to fulfil the condition necessary to demonstrate the heredity of any infectious disease in man, and when we speak of the heredity of these maladies in the higher animals it is to be recalled that we are using the term "heredity" rather loosely. No parasitic disease is known to be hereditary in man, though we know of several diseases in lower animals (as in insects and ticks) which are hereditary in a stricter sense of the term; namely, the sexual products are infected before fertilization occurs. Several parasites (example, hookworms, *Schistosoma japonicum*) have been reported in the new-born; in these cases, infection[1] has been acquired *in utero*, hence these represent instances of "congenital infection," not of "heredity" of parasites.

Influence of Parasites upon Their Hosts.—Views regarding the injurious effects of parasites have passed from extreme to extreme, some authors going so far as to attribute to some parasites injurious actions which they surely do not have, and others going so far in the opposite direction as to see in the parasites a supposed advantage or even a neces-

[1] The words "*infection*," "*infestation*," and "*contagious*," have various meanings in literature. Properly speaking "to infect" (from *inficere*) means to put into, to taint, as in even a very light case of tuberculosis; *infest* (from *infestare*) involves an idea of numbers, as in a heavy infection with tuberculosis; *contagious*, according to some authors (and a decision which the U. S. Supreme Court rendered upon thoroughly inadequate scientific data), refers to a disease contracted by *contact with a patient*, but according to the view expressed in the regulations of the U. S. Public Health Service it is synonymous with *communicable, i. e.*, a disease communicated by *contact with contagium* (*i. e.*, infectious material).

sity to the host. Let us recall, however, that the injury done may vary with the species, size, location, and number of the parasites, and with the condition and age of the host. This injury may be accomplished in various ways: (1) Nourishment is taken which should go to the host; (2) blood is taken by the parasite as food; (3) mechanical pressure irritates or destroys organs, tissues, or cells; (4) natural channels may be obstructed; (5) the wandering of the parasite may cause irritation; (6) substances may be excreted which have a toxic influence, and which may change the natural condition of the body fluids (blood); (7) injury to the intestinal mucosa or to the skin may form points of entrance for bacterial and protozoan infections; (8) injury to various organs may result in other secondary disturbance.

Such injury does not, as a rule, go on increasing indefinitely in any geometrical progression because of succeeding generations of parasites, for the general rule obtains (with a few exceptions, as in infections with certain protozoa, the vinegar eel, and some of the mites) that *for every adult animal parasite found in the human body a separate embryo or larva must enter*. Thus, hookworms do not multiply generation after generation in the intestine, but the eggs must leave the host and the resulting larvæ reënter the body in order to become adult.

Concurrent Parasites and Cancer.—That the presence of parasites is occasionally associated with cancer has been known for many years. Thus, flukes (*Clonorchis, Opisthorchis, Schistosoma haematobium, S. mansoni*), larval tapeworms (*Cysticercus, Echinococcus*), roundworms (*Trichinella, Gongylonema,* ? *Thelazia*), and mites (*Demodex*), have all been reported in association with cancerous growth. *Gongylonema* is commonly associated with cancer of the stomach in rats. The experimental production of cancer of the liver by *Cysticercus*, the cumulative reports of concurrent cancer and various parasites, the recent reports of cases of *Gongylonema* in man, the frequency of cancer in the organs which *Gongylonema* infects, and the distribution of its intermediate hosts, have all combined to lead parasitologists to wonder whether there is in reality ground for a generalization on the correlation of cancer and animal parasitism; but it took the courage of a Sambon (1924; 1925) to direct attention prominently to this speculation. That there is sufficient basis for pursuing the thought further is beyond question; but in connection with the inevitable studies along this line, the history of parasitology suggests extreme though open-minded conservatism.

Concurrent Parasites and Appendicitis.—That parasitic infections (*Endamoeba*, ascarids, hookworms, pinworms, whipworms, *Schistosoma*, tapeworms) occur in many cases diagnosed as or confused with appendicitis cannot well be questioned. That some attacks of recurrent appendicitis (or pseudoappendicitis?) are synchronous with the passage of tapeworm segments and that the attacks subside after the segments escape, may be conservatively admitted. But data are lacking which would justify the conclusion that appendicitis is dependent upon animal parasitism.

Concurrent Parasites and Pneumonic Symptoms.—That infection with ascarids has at times been confused with pneumonia is beyond doubt, and

both biological data and experimental clinical evidence are now available to show that certain parasitic infestations (ascarids, hookworms, *Strongyloides*) which are more common in rural than in urban localities, and more common in warm and moist than in cold and dry areas, and in general more common in children than in adults, have a pulmonary stage which is to be considered by the clinician in endemic areas in connection with patients (especially children) who are developing what may appear to be a pneumonia.

Generic and Specific Infections.—Infections may be identical or distinct generically or specifically. These terms are used in their zoölogical sense, to express more accurately the relation which the diseases of man bear to those of animals. Thus it has been reported that *Taenia solium* occurs in both man and dog; if this statement were correct, the dog would be a very important factor, from a public health "point of view," in spreading *T. solium* and cysticercosis. The reported presence of this parasite in dogs is, however, based upon an error of identification, for there is a tapeworm belonging to the genus *Taenia* that does occur in dogs but it belongs to a species (*T. hydatigena*) specifically distinct from but quite closely (generically) related to *T. solium*. Hence, man and dogs, in this instance, have infections which are *generically* identical, since both parasites belong to the same genus, but *specifically* distinct, since the two worms represent distinct species (*T. solium* and *T. hydatigena*). On the other hand there is a specifically identical tapeworm-infection (*Dipylidium caninum*) which is common to dogs and cats and which occurs in man.

Diagnosis of Parasitic Diseases.—The general rule obtains that the best method of diagnosing most parasitic diseases is by a microscopic examination: examine *sputum* for suspected parasitic diseases of the lungs; *feces* for suspected parasitic infections of the intestine and liver; *urine* for suspected parasites of the kidney or bladder; *blood*, *feces*, and *urine*, for suspected parasitic diseases of the circulatory system; *blood* and *muscle* for suspected infections of the muscle; *blood* for suspected infections of the lymphatic system. In some cases a diagnosis can be made by a gross examination of the feces. In some parasitic diseases, diagnosis can be safely made upon symptoms, especially if the patient is within the endemic area of a given malady. The technique of fecal examinations can best be given here.

In *gross* examinations of the stools (for pinworms, hookworms, etc.) the feces should be shaken up well with warm water and allowed to settle; pour off any floating material and wash the stool in this manner several times; the worms will thus be concentrated. Or, place the stool in a piece of cheese cloth or in a fine sieve, and run water through this until the worms are freed from the fecal material.

For *microscopic* examination of feces, take a small portion of fecal matter on the end of a match or toothpick, using a separate one for each stool; smear this in a drop of water on a slide; cover with an ordinary cover-glass, avoiding unnecessary pressure, and examine ten such preparations.[1] Or, strain the feces (through cheese cloth or wire screen),

[1] For a bulletin by Hall, giving a summary of different methods, apply to U. S. Bureau of Animal Industry.

then centrifuge and examine the sediment. Or, use a "flotation" method, namely, the fecal sample is first strained, then stirred in a fluid with a specific gravity higher than that of the eggs, as saturated salt solution, or equal parts of a glycerin and a saturated solution of magnesium sulphate; the eggs float to the top which is skimmed off and examined microscopically, or if a slide is placed in contact with the top, the eggs will adhere to the glass.

For eggs with thick shells (whipworms, large tapeworms, flukes), use a strong illumination; for worms with thin shells (hookworms, pinworms, etc.), use a more moderate illumination; examine first with medium magnification (8 mm. or $\frac{1}{3}$-inch focal length), later with higher power, for more exact determination. Microscopic examinations for the common intestinal worms are made free of charge by all Southern State Boards of Health in the United States.

To make permanent mounts of eggs, preserve the material in alcohol; then transfer to 95 parts alcohol plus 5 parts of glycerin; allow the alcohol to evaporate slowly, and when evaporated to glycerin, mount the material in glycerin-jelly.

Serodiagnosis, by the precipitin test or complement fixation, is used in several parasitic infections, especially hydatid disease.

Treatment.—The *general* rule obtains that for verminous infections of the brain, bones, muscles, eye, lungs, liver, kidneys, spleen, blood, and lymphatics, there is no satisfactory specific medicinal treatment, although some of these cases may be treated surgically; some may be treated intravenously with tartar emetic. Intestinal, bladder, and some skin infections by parasites are treated medicinally.

Prevention.—So far as most verminous parasites in temperate climates are concerned, ordinary habits of cleanliness; ordinary care in preparing food; ordinary methods of meat inspection; a proper disposal of alvine discharges—as in sewers, or properly constructed privies; and a recognition of the fact that the dog is not a human being, are in themselves sufficient to prevent serious trouble (in form of epidemics) from most parasites. In warm countries protection against mosquitoes will reduce certain parasitic affections (malaria, filariasis).

Personal Rules of Hygiene.—(1) The use of spring, boiled, or filtered water tends to decrease certain protozoan, fluke, and roundworm infections; (2) proper care of meat (protection from flies) and thorough cooking protects against certain dipterous larvæ, certain tapeworms, trichinosis, and certain protozoa; (3) avoidance of depraved tastes for insects aids in protecting against certain tapeworms and thorn-headed worms; (4) keeping the hands and nails clean, especially after handling dogs, aids in protecting against a certain tapeworm, hydatid disease and tongueworm; (5) personal cleanliness after defecation aids in protecting against auto-infection with pinworms and *Cysticercus cellulosae;* (6) wearing shoes in infected areas helps to protect against hookworm infection, *Strongyloides*, and the burrowing flea.

Public Rules of Hygiene.—(1) If sewage is used for fertilizing, it is best to grow upon the land, so fertilized, only grass, cotton, or such vege-

tables as are subjected to cooking before eating; (2) properly dispose of all feces, especially in schools, churches, asylums, hospitals; (3) interdict nuisances, especially in warmer climates, and upon plantations, in mines and in digging tunnels and canals; (4) meat inspection in the local slaughter houses (the federal inspection covers abattoirs licensed for interstate trade); (5) segregate local slaughter houses and place them under the supervision of a competent veterinarian, who might well be a member of the local board of health; (6) keep swine in a less swine-like manner, especially see that the privy is not near the pig-pen; (7) swine-offal and swill should be cooked in case they are fed to hogs; (8) destroy all ownerless dogs, and keep dogs away from slaughter houses—the dog pound is an institution of practical public health importance.

CLASSIFICATION OF ANIMAL PARASITES

The parasites do not represent a group of animals closely related to each other systematically, but rather several diverse groups, more or less widely separated but with somewhat similar biological habits. For the details of classification[1] the reader is referred to works on systematic zoölogy; for this article, we may divide the animal parasites as follows:

1. Unicellular animals (without tissues), as the parasites of malaria . *Protozoa*, p. 502
   Pluricellular animals (with tissues), metazoa 2
2. Body more or less flattened dorso-ventrally 4
   Body ordinarily round in transverse section 3
3. Body never annulated; never provided with legs; jaws absent 5
   Body annulated, or at least provided with mouth parts; usually breathe through a tracheal system; adults with jointed legs or other appendages . . . 7
4. Intestine, but no anus, present; one or two suckers present; body not segmented; parasitic in liver, lungs, blood, intestine, occasionally elsewhere; flukes *Trematoda*, p. 506
   Intestine absent; two or four suckers on head; body of adults segmented; tissue usually contains calcareous corpuscles; adults (tapeworms) parasitic in intestine; larvæ (bladder worms) parasitic elsewhere . . . . *Cestoda*, p. 531
   Intestine and anus present; sucker on posterior end; body annulated like an earthworm; parasitic in upper air-passages, or externally; leeches, blood suckers . . . . . *Hirudinea*, p. 608
5. Intestine absent; armed rostellum present; very rare in man, in intestine; thorn-headed worms . . . . . *Acanthocephala*, p. 588
   Intestine present; no armed rostellum . . . . . *Nematoda* 6
6. Intestine rudimentary in adults; lateral chords absent; rare, accidental parasites in intestine of man; hair snakes or horse-hair worms . . . *Gordiacea*, p. 588
   Intestine present; lateral chords present; parasitic in intestine, muscles, lymphatics, etc., very common and important; roundworms . *Eunematoda*, p. 558
7. Six legs present in adult; wings present in most species; larva annulated much like an earthworm; breath through trachea; adults ectoparasites; occasionally larva is parasitic under skin, or in wounds, or an accidental parasite in the intestine or bladder; insects . . . . . *Insecta*, p. 619
   Eight legs present in adult, six legs in larva; head and abdomen coalesced; ectoparasites; some burrow under the skin or live in the hair follicles; acarines *Acarina*, p. 609
   Four claws around the mouth; larva encysted in various organs; adult occasionally parasitic in nasal passages; tongueworms . . . *Linguatulidae*, p. 618
   Numerous legs present; occasionally accidental parasites in nasal passage or intestine; thousand leggers . . . . . *Myriapoda*, p. 619

[1] The U. S. Public Health Service is publishing a series of bulletins giving the classification (to genera) of all animal parasites reported *for man.*

TABLE OF PARASITIC INFECTIONS OF MAN, ARRANGED ACCORDING TO COMMON LOCATION IN BODY

(* *Contains species reported as indigenous, for man, in the United States or Canada.*)
(† *No species known as indigenous, for man, in the United States or Canada.*)

APPENDIX.—* *Endamoeba*, p. 503. † *Schistosoma*, p. 520. * Ascarids, p. 577; * hookworms, p. 558; * pinworms, p. 581; * whipworms, p. 585.

BLADDER.—† *Schistosoma*, p. 520. * *Sparganum*, p. 557. * *Anguillula*, p. 607; * *Agamomermis*, p. 608.

BLOOD.—* *Balantidium*, p. 504; † *Trypanosoma*, p. 503; *Schizotrypanum*, p. 503; * malaria, p. 504; * *Plasmodium*, p. 504. † *Hexathyridium*, p. 516; † *Schistosoma*, p. 520. * *Microfilaria*, p. 599. Also young stages of various worms in transit.

BRAIN.—† *Paragonimus*, p. 506; † *Schistosoma*, p. 520. * *Cysticercus*, p. 550; † *Coenurus*, p. 522; † *Multiceps*, p. 552; * *Sparganum*, p. 557.

DERMAL.—† *Leishmania*, p. 503. * Mites (* itch, p. 611; * hair follicle, p. 615; * jigger, p. 616; * straw itch, p. 616; * ticks, p. 609; etc., p. 618).

EAR.—**Otobius*, p. 610; * spinose ear tick, p. 610.

ESOPHAGUS.—* *Gongylonema*, p. 587; † *Physaloptera*, p. 584.

EXTERNAL.—* Ticks, p. 609. * Bed-bugs, p. 622; * fleas, p. 619; * lice, p. 621; various insects, p. 623.

EYE.—† *Agamodistomum*, p. 530; † *Monostomulum*, p. 530. * *Cysticercus*, p. 550; * *Sparganum*, p. 557. † *Agamofilaria*, p. 607; † *Filaria*, p. 607; † *Habronema*, p. 607; † *Setaria*, p. 607.

Generalized (more or less) somatic infections. † *Leishmania*, p. 503; * *Rhinosporidium*, p. 504; † *Paragonimus*, p. 506; † *Schistosoma*, p. 520. * *Cysticercus*, p. 550; * *Echinococcus*, p. 552; * *Sparganum*, p. 557. * *Filaria*, p. 599; * *Trichinella*, p. 588. † *Armillifer*, p. 619; † *Linguatula*, p. 618; * *Porocephalus*, p. 619.

Heart.—* *Cysticercus*, p. 550. *Dirofilaria*, p. 606.

Intestine.—* *Caconema*, p. 582; † *Haemonchus*, p. 585; * *Heterodera*, p. 582; † *Mecistocirrus*, p. 585; † *Oesophagostomum*, p. 584; † *Physaloptera*, p. 584; * *Rhabditis*, p. 585; † *Ternidens*, p. 584. † *Chordodes*, p. 584; † *Gordius*, p. 588; * *Paragordius*, p. 588. † *Echinorhynchus*, p. 588; † *Macracanthorhynchus*, p. 588; † *Moniliformis*, p. 588. Various insect larvae, p. 623.

INTESTINE, LARGE.—*Balantidium*, p. 504; * *Endamoeba*, p. 503. † *Gastrodiscoides*, p. 520; † *Gastrodiscus*, p. 520; † *Schistosoma*, p. 520; † *Watsonius*, p. 520. * *Pinworms*, p. 581; * *Oesophagostomum*, p. 584; * *Trichuris*, p. 585; whipworms, p. 585.

INTESTINE, SMALL.—* *Chilomastix*, p. 503; * *Councilmania*, p. 503; † *Eimeria*, p. 504; * *Endamoeba*, p. 503; * *Endolimax*, p. 503; * *Giardia*, p. 503; † *Isospora*, p. 504; * *Trichomonas*, p. 503. † *Artyfechinostomum*, p. 519; † *Clonorchis*, p. 510; † *Echinochasmus*, p. 519; † *Echinostoma*, p. 519; † *Euparyphium*, p. 519; † *Fasciolopsis*, p. 519; † *Heterophyes*, p. 519; † *Metagonimus*, p. 520; † *Opisthorchis*, p. 514; † *Stamnosoma*, p. 520. † *Bertiella*, p. 541; † *Braunia*, p. 544; † *Davainea*, p. 540; † *Diplogonoporus*, p. 544; * *Diphyllobothrium*, p. 541; * *Dipylidium*, p. 541; † *Drepanidotaenia*, p. 540; † *Hydatigera*, p. 438; * *Hymenolepis*, p. 538; † *Ligula*, p. 544; † *Raillietina*, p. 540; * *Taenia*, p. 532; * *Taeniarhynchus*, p. 532. *Ancylostoma*, p. 561; * ascarids, p. 574; *Enterobius*, p. 581; * hookworms, p. 558; † *Necator*, p. 560; *Oxyuris*, p. 581; * pinworms, p. 581; * *Strongyloides*, p. 575; *Syphacia*, p. 582; *Toxascaris*, p. 578; *Toxocara*, p. 578; *Trichinella*, p. 588; *Trichostrongylus*, p. 585.

KIDNEY.—* *Echinococcus*, p. 552. † *Dioctophyme*, p. 608.

LIVER.—* *Endamoeba*, p. 503. † *Clonorchis*, p. 510; † *Dicrocoelium*, p. 516; † *Fasciola*, p. 516; † *Opisthorchis*, p. 514. † *Schistosoma*, p. 520. * *Echinococcus*, p. 552. * Ascarids, p. 577; † *Physaloptera*, p. 584. † *Armillifer*, p. 619.

LUNGS.—* *Endamoeba*, p. 503; * *Trichomonas*, p. 503. † *Fasciola*, p. 509; † lung flukes, p. 506; † *Paragonimus*, p. 506. * *Hydatids*, p. 552. † *Metastrongylus*, p. 595. Also larval stages of * hookworms, p. 558, * *Strongyloides*, p. 575. and * ascarids, p. 577.

LYMPHATIC SYSTEM.—* *Filaria*, p. 599; *Wuchereria*, p. 600. Also young stages of various worms in transit.

MOUTH (cavity and membrane).—* *Endamoeba*, p. 503; * *Trichomonas*, p. 503. * *Agamomermis*, p. 608; * *Gongylonema*, p. 587. Insect larvae, p. 587.

MUSCLES.—† *Sarcosporidia*, p. 504. *Coenurus*, p. 552; * *Cysticercus*, p. 550; † *Multiceps*, p. 552. * *Trichinella*, p. 588.

NASAL PASSAGE.—Thousand leggers, p. 619; * screw-worms, p. 623.

PHARYNX.—† *Fasciola*, p. 517. Various worms in transit.

STOMACH.—*Dicrocoelium*, p. 516; *Fasciola*, p. 516. † *Anguillulina*, p. 585: † *Haemonchus*, p. 585. Also stages of intestinal parasites in transit.

SUBCUTANEOUS.—* *Cysticercus*, p. 550; * *Sparganum*, p. 557. * *Agamofilaria*, p. 599: † *Gnathostoma*, p. 595: † guinea-worm, p. 596; † *Lagochilascaris*, p. 595; † *Loa*, p. 598; † *Onchocerca*, p. 597; † *Rhabditis*, p. 595.

VAGINA.—* *Trichomonas*, p. 503. † *Schistosoma*, p. 520. † *Leptodera*, p. 608; * pinworms, p. 581.

NOMENCLATURE AND TERMINOLOGY

To the biologist, *nomenclature* deals with the *names* used to designate systematic units, such as families (*Taeniidae*), genera (*Tænia*), species (*Taenia saginata*), etc. As systematic zoölogists are obliged to use thousands upon thousands of technical names, it is advisable that these should be removed, so far as possible, from the influence of individual or national tastes and prejudices; and, to make them international in character, Latin has been adopted as the basis for all *technical* names (as opposed to *vernacular* names). The acceptance or rejection of names and the method of writing them are governed by "codes of nomenclature." For the zoölogists, the International Congress has adopted "International Rules,"[1] prepared by a permanent international commission of eighteen members. This code is based primarily upon the rules proposed by Linnaeus, in 1751, modified to meet advances in science. In order that no revolutionary principle may be suddenly introduced, the rules of the Congress provide that no proposition for changing the code can be adopted unless submitted to the Commission at least one year prior to the tri-annual meeting of the Congress. The chief points in the code are: (1) The "law of priority," which provides that the *valid* name for any genus or species is its oldest *available* name, *i. e.*, available under the code; thus, *Ascaris*, 1758, is an older name than *Fusaria*, 1800, for the ascarids. (2) The "rule of homonyms," which provides (*a*) that when two generically distinct animals have received the same generic name, this name is available only for the earlier genus (thus, when *Trichina* was proposed for a genus of worms by Owen in 1835, it was already in use for a genus of insects, 1832, hence the name cannot be adopted for the worm); and (*b*) that when two species in any given genus have received the same specific name, it is available only in its earlier use (thus, *Taenia murina*, 1845—*Hymenolepis nana*, 1852—is antedated by *Taenia murina* Gmelin, 1790—*Cysticercus fasciolaris*—hence *murina*, 1845, is not available as a name for the dwarf tapeworm, and *nana*, 1852, its oldest synonym becomes valid). (3) No name can be changed because of its inappropriateness or for any subjective reason, as *names are not definitions*, hence the introduction of *Amoeba dysenteriae* for *Amoeba coli* was not permissible under the code.

Physicians will do well to acquaint themselves with the rules, before they publish or change zoölogical names, as it is often difficult to understand whether or not a physician is using a new name in a zoölogical sense, and further, because names are too frequently proposed contrary to zoölogical customs.

Terminology, in distinction to nomenclature, deals with the technical *terms* of parts, organs, functions, conditions, etc. No recognized code of rules governs the names of the muscles of the body or the names of diseases. A man adopts a technical term because it has been taught to him, or he changes it, if a better name occurs to him, and, finally, men

[1] See Stiles, 1905, pp. 1 to 50, the "International Code of Zoölogical Nomenclature as applied to Medicine." *Bulletin* 24, *Hygienic Laboratory, U. S. Public Health Service*, Washington. See also Proceedings on the Ninth International Zoölogical Congress of 1913.

adopt the names best known to them or names agreed upon by some committee. Thus, terminology is largely subjective, and such incongruities occur as using a term like "spotted fever" for two or three different diseases.

For parasitic diseases we may distinguish three different kinds of terms in particular: (1) Latin terms based upon the zoölogical generic names (as *distomatosis, taeniasis, trichinosis, acariasis, etc.);* (2) vernacular terms based upon some symptom, locality, etc. (itch, Egyptian hematuria); (3) vernacular terms based upon a vernacular name of the parasite (hookworm disease). For international use, Latin terms are by all means preferable, as they need not be translated, but for current use vernacular terms are often very convenient.

Bibliography.—In a short article of this kind it is impossible to give a full bibliography, for which the reader is referred to Huber's *Bibliographie der klinischen Helminthologie* (1895, 1898, 1899–1900), or Stiles and Hassall's Index Catalogue of Medical and Veterinary Zoölogy (*Bull.* 39, *U. S. Bureau of Animal Industry*).

For annual reviews of literature on parasites, see especially *Zoölogical Record* and *Archiv für Naturgeschichte.* For current literature, with original articles, reviews, and current bibliographies, see especially *Archives de Parasitologie, Annales de Parasitologie, Centralblatt für Bakteriologie, Journal of Parasitology, Tropical Diseases Bulletin, Zoölogischer Anzeiger,* and *Zoölogischer Bericht.* The current zoölogical references can be purchased in card form from the Concilium Bibliographicum, Zurich. The most extensive card catalogue on the subject is the combined index in the Zoölogical Division of the U. S. Public Health Service and the U. S. Bureau of Animal Industry.

Determination of Specimens.—Specimens of animal parasites of man are determined for physicians, free of charge, by the Hygienic Laboratory, U. S. Public Health Service, Washington, D. C. Such material should be forwarded in alcohol (about 50 to 70 per cent.) or formalin, 5 per cent. All carriage expenses are to be prepaid.

Government Publications.—For U. S. Government publications on animal parasites, application should be made to the "Superintendent of Documents, G. P. O.,Washington, D. C.," or (either directly or through a Senator or Congressman) to the Chief of the Bureau by which the document was issued.

Laboratory Work in Colleges.—As many of the parasites of dogs, cats, rats, and swine are either specifically or generically identical with the parasites of man, fresh material can be obtained from these animals. Fecal material, containing hookworm eggs, can frequently be obtained from the various Southern Boards of Health.

PROTOZOAN PARASITES[1]

In general terms, not without exceptions, the smaller the cross-section of a specific organism the more numerous are the individuals of that

[1] For descriptions of the genera and list of species, see Stiles and Hassall, 1925 *a*, Key-Catalogue of the Protozoa reported for man, Bull. 140, Hyg. Lab., Washington, pp. 1–63.

species. Thus, to use an extreme comparison, there are more individual specimens of *Bacillus coli* than of African elephants, in the world.

Protozoa are usually very small, often invisible to the naked eye. Accordingly, as compared with tapeworms, it is to be expected, on general principles, that protozoa are to be found more commonly in the human body than are tapeworms, and this expectation is fully realized. Not unnaturally, their frequency and number have been noticed in cases of various diseases and the thought has arisen that they may be the causes of the diseases in question; but, because of their size and concurrently their great frequency and large numbers, it seems logical to conclude that it would really be remarkable if certain protozoa were not found in patients suffering from various diseases, for they are present in a very high percentage of people. Special conservatism is therefore advisable in attributing a given disease to any given protozoön or to a structure interpreted or misinterpreted as a protozoön.

In general, the protozoa are to be divided into rhizopods (with pseudopodia), flagellates (with flagella), sporozoa (cell membrane present), and ciliates (cilia present.)

Rhizopod Parasites of Man.—That amœbic dysentery and amœbic abscess are caused by at least one amœba (*Endamoeba histolytica*) is not to be doubted in view of present knowledge; but it is equally true that a considerable proportion (5 to 20 per cent., etc.) of a given population may, as "carriers," harbor this organism without showing symptoms. Some authors admit the existence of an amœbic appendicitis, others an amœbic cutaneous ulcer, others an amœbic arthritis deformans, and amœbic lymph glands in Hodgkin's disease, as due to the same parasite.

Some amœbæ (*Councilmania lafleuri, Caudamoeba sinensis, Craigia hominis*, etc.) are *sub judice* as respects their zoölogical and pathogenic status; still others (*Endamoeba coli, E. gingivalis, Endolimax nana, Iodamoeba williamsi, Dientamoeba fragilis, Vahlkampfia* various species, *Karyamoebina falcata, Hartmanella hyalina, Sappinia diploidea, Wasielewskia gruberi*, etc.) are more or less common in man but are generally viewed as non-pathogenic.

Flagellate Parasites of Man.—Few organisms are more difficult to study than are the flagellates. Not unnaturally, therefore, there is considerable confusion in respect to those observed in man. The following may be considered as definitely non-pathogenic or at most very doubtfully pathogenic: *Oicomonas, Pararhizomastix, Monas, Bodo, Prowazekia, Cercomonas, Diplocercomonas, Enteromonas, Embadomonas, Tetrachilomastix, Tetramitus, Copromastix, Octomitus, Hexamita, Ditrichomastix.*

The following forms are to be considered as definitely pathogenic in man: *Leishmania* in tropical ulcer and kala-azar; *Trypanosoma* in African sleeping sickness; and *Schizotrypanum* in Chagas disease of South America. These three genera are, at present, practically unimportant to the North American practitioner, though of great theoretical interest to certain specialists.

Certain other flagellates are at present in dispute as respects their pathogenicity (all in flagellate diarrhœa): *Chilomastix mesnili, Trichomonas* (sensu lato) *confusa*, and *Giardia lamblia*. A considerable number

of cases of flagellate diarrhœa have been reported but have not yielded very satisfactorily to treatment. Experimental studies (by Hegner) on rats, apparently confirmed in a limited number of clinical cases in man, seem to indicate that a change to a predominantly meat diet may be the treatment of choice in the future. Diagnosis can be made only microscopically.

Spirochaetacea of Man.—The question as to whether the spirochetes are protozoa or bacteria is still *sub judice*. Various, rather poorly defined, genera (*Treponema, Borrelia,* and *Leptospira*) with numerous species are reported for man. See the special articles on syphilis (*Tr. pallidum*), yaws (*Tr. pertenue*), relapsing fevers (*Borrelia recurrentis,* etc.), yellow fever (*Leptospira interrogans* seu *icteroides*), West African tick fever (*B. duttoni*), S. American tick fever (*B. venezuelensis*), infective jaundice (*B. icterohaemorrhagicae*), rat-bite fever (*B. morsus-muris*), and Vincent's angina (*B. vincenti*). Numerous other species or supposed species are reported for man.

Sporozoa of Man.—Malaria is the classical example of sporozoan disease in man; but, theoretically, some authors classify the malarial parasites as flagellates: *Plasmodium malariæ* of quartan malaria, *Pl. vivax* of tertian malaria, *Laverania falciparа* of estivo-autumnal malaria. Anopheline mosquitoes are the vectors.

Rhinosporidium seeberi, found in nasal polypi, ear, eye, and penis, As usually classified as a sporozoön, but recent studies indicate that the parasite is a lower fungus.

Sarcosporidia, very common in swine and sheep, are occasionally found in the muscles of man on autopsy. Symptomatic diagnosis is unknown and antemortem diagnosis would be purely accidental. Treatment is at present theoretically impossible. It is important not to mistake Sarcosporidia of hogs for trichinæ when one is testifying in court.

Coccodiosis.—Various coccidia have been reported for the intestine of man. The diagnosis is by microscopic examination of the feces. The species reported for man are: *Isospora bigemina, I. hominis, Eimeria oxyspora, E. snijdersi, E. stiedae,* and *E. wenyoni.* In various animals, coccidia produce an intense, even fatal, diarrhœa. Treatment is unknown.

Numerous pseudococcidia have been reported for man.

Of the Hematozoa, in addition to the malaria parasites, *Pyroplasma hominis* has been reported in Rocky Mountain spotted fever, *Theileria tsutsugamushi* in Tsutsugamushi disease of Japan, *Bartonella bacilliformis* in Oroya fever of Peru, *Paraplasma flavigenum* in yellow fever, *Toxoplasma pyrogenes* in the tropics, and *Histoplasma capsulatum* in lymph nodes, Panama. Of these six supposed hematozoa, all but *Bartonella* have been placed *sub judice,* or even rejected; and even *Bartonella* is *sub judice* as respects its position in classification.

Ciliates of Man.—Ciliates are swallowed with the drinking water or in encysted stage with contaminated food. Occasionally, ciliates in tap water used in making smears of feces for microscopic examination are mistaken for parasites.

Of the various species reported for man, only one (*Balantidium coli*) appears at present to have a definite pathogenic status (balantidial

diarrhœa), while *Chilodon dentatus, C. uncinatus, Colpoda cucullus, C. steini, Uronema caudatum, Bursaria* species, *Balantidium giganteum, B. minutum, Nyctotherus africanus, N. faba,* and *Vorticella* species, are either contaminations, errors of interpretation, or so rare as parasites that they appear to be of importance to the clinician only as possible sources for error in diagnosis.

Miscellaneous Protozoa and Pseudoprotozoa.—In many infections of man ascribed to protozoa, the evidence thus far submitted has not been sufficient to carry general concensus of opinion that the interpretations are correct.

The supposed protozoan parasite of smallpox has been described as belonging to a genus variously named as *Amöbosporidium, Cytorhyctes, Protobios, Sporidium,* and *Strombodes.*

The supposed protozoon of hydrophobia has been described as *Encephalitozoön, Neuroryctes,* and *Protobios.*

The supposed protozoan parasite of cancer has been described as *Karyophagus, Rhopalocephalus,* and *Unicellula.*

Blastocystis, supposed protozoön, is apparently a plant cell.

Coccidioides, a serious parasite of the skin, and formerly classified as possibly a protozoon, is now classified as an ascomycete (plant).

Cyclasterion, the supposed protozoön of scarlet fever, is now considered to be possibly an artefact, possibly a chlamydozoön but not connected with the disease.

The supposed parasite of Rocky Mountain spotted fever which has been named *Dermacentroxenus rickettsi* is also classified as a *Rickettsia.*

Dengue has been attributed to a special protozoön called *Plasmoeba* and also to a *Leptospira.*

Certain bacteria-like organisms, called *Rickettsia* may possibly be protozoa, but this is doubtful. In this genus have been classified supposed parasites of quintana (five-day fever) and of typhus—both transmitted by lice—and also the supposed parasite of Rocky Mountain spotted fever.

Various other protozoa or alleged protozoa have been reported for man but for the present, at least, they are of no interest to the practitioner.

In general it may be said that a certain few protozoa are known to be of very extreme importance as cause of disease, more especially in the tropics; a few additional protozoa are of secondary importance from a clinical viewpoint, but the present evidence is that they may cause diarrhœa; some additional parasites (the Spirochaetacea) frequently classified as protozoa may in reality be bacteria; a number of alleged protozoa, described as cause of serious diseases, may perhaps not be protozoa at all; some parasites once supposed to be protozoa are now known to belong to the plant kingdom; and numerous protozoa described as parasitic in man are either of no known medical importance or they are too inadequately described to be definitely recognized.

Intensely interesting as the protozoa are, zoölogically, there is a (probably not unnatural) tendency to emphasize their importance in human medicine beyond the point of demonstrated fact. In comparative medicine many serious diseases have been traced to protozoa.

DISTOMATOSIS—TREMATODE OR FLUKE INFECTIONS[1]

Terminology.—The general term *distomatosis* or *distomiasis* is based upon *Distoma*, which has been used by many authors as the collective genus for the trematodes, more especially for the so-called digenetic forms. As a generic name for these parasites *Distoma* is not valid and the species which have been included in this genus are now distributed over a large number of well-defined genera. Upon the names of these more restricted genera, Latin terms have been based to designate infections with species of the respective genera (as *fascioliasis, clonorchiasis, opisthorchiasis, paragonimiasis, schistosomiasis*). The word "distomatosis" has been combined with the name of the organ affected (as pulmonary distomatosis); while for some of the diseases, there are well-known vernacular terms (liver-fluke disease, liver rot, etc.).

Trematode Diseases in Man.—There are four different clinical classes of trematode diseases which may be regarded as typical, in the sense that in these four instances the infection of man by certain trematodes is more or less normal in the life-cycle of the parasite under consideration. These are: (1) pulmonary distomatosis, with cerebral or other infection as secondary; (2) hepatic distomatosis, with splenic or intestinal infection as secondary; (3) intestinal distomatosis; and (4) blood distomatosis with cerebral infection as secondary. In addition we find recorded rare instances of (5) ophthalmic distomatosis, which may be an accidental secondary form of hepatic distomatosis.

All of the parasites in question, with the exception of the blood-flukes, are hermaphrodites; all possess an oral or an oral and a ventral sucker, a mouth, and two blind intestinal ceca. The life-cycle is quite complicated and may involve two or more generations which live outside of man. The parasites require at least one intermediate host or in some cases two.

PULMONARY DISTOMATOSIS—LUNG-FLUKE DISEASE

Paragonimiasis or Parasitic Hemoptysis.—Geographical Distribution.—The Asiatic region, particularly Japan, China, and Formosa, appears to be the special home of this disease in man, although a generically related if not specifically identical infection occurs also as an endemic disease in hogs, dogs, and cats in the United States. The infection for man is reported also for the Philippines, Korea, Peru, Yucatan, and Mexico, and occasionally imported cases are found in other places, as in the United States.

Zoölogical Distribution.—It is difficult to determine the original host of this disease which is known to occur more or less frequently in man, cats, tigers, dogs, swine; and Looss (1905) says it occurs in cattle. Pulmonary distomatosis is occasionally found in cattle and man as an accidental manifestation of fascioliasis, and lung infection with other genera of flukes is exceedingly common in snakes, toads, and frogs.

[1] For detailed index to subject, see *Bulletin* 37, *Hygienic Laboratory*.

For descriptions of the genera and list of species, see Stiles & Hassall, 1926 a, Key-Catalogue of the worms reported for Man *Bulletin* 142, *Hygienic Laboratory*.

The Parasite.—*Paragonimus westermanii*[1] (Kerbert, 1878) is a plump, depressed, oval, or pyriform, pinkish to reddish-brown (live specimens), spinose fluke, 7.5 to 16 mm. long by 4 to 8 mm. broad by 2 to 5 mm. thick; with branched testicles and ovary but unbranched intestinal ceca; eggs yellow, 77 to 102.5 by 40 to 75 μ with distinct operculum but containing no miracidium when discharged. The adult parasites are found in cysts, one to three together, in the lungs, especially in upper lobes, occasionally in the pleura, liver, abdominal cavity, brain, orbit, lower eyelid, cervical glands, scrotum, and other parts of the body.

Source of Infection.—The eggs which are passed in the sputum or the feces of man develop a ciliated miracidium (embryo) which escapes from the egg shell into water, in sixteen days (in summer) to sixty days in winter; this embryo bores into any one of several snails (reported as *Ampularia luteostoma; Melania ebenina, M. extensa, M. gottschei, M. libertina, M. nodiperda, M. n. quinaria, M. obliquegranosa, M. paucicincta, M. tuberculata*) in which the later stages (sporocyst, redia, cercaria) develop; the cercaria escapes from the snail into water, enters any one of several fresh water crustacea (reported as *Astacus japonicus* seu *similis; Eriocheir japonicus; Potamon dehaani, P. obtusipes, P. sinensis; Pseudotelphusa iturbei; Sesarma dehaani*) and encysts as a "metacercaria," which forty-two to fifty-four days later, upon being swallowed, is the infective stage for man, etc. The metacercariæ escape from this cysts, perforate the intestinal wall and are said to remain in the abdominal or thoracic cavity about thirty days (in experimental cats or dogs), then to migrate into the lungs, and arrange themselves in pairs in the bronchioles, which they hypertrophy and form into cysts.

Frequency.—More frequent in mountainous localities (Katsurada); chiefly in peasants, more common in males than in females (88.57 per cent. to 11.43 per cent. in 481 collated cases) and between the ages of sixteen and thirty years; in some localities 20 to 73 per cent. of the lung-fluke patients give a history of other cases in the same family (Katsurada), while in other places the family history is reported as negative. It is stated that in certain parts of Formosa, 15 to 50 per cent. of the inhabitants is affected; in one Japanese village nearly all the inhabitants harbor the parasite (Baelz.) In a hospital in Okayama, 0.4 per cent. of the 20,793 patients from 1891 to 1897 showed infection (Inouye). Various Japanese physicians report that from 2 to 14 per cent. of their patients suffering from respiratory troubles harbor this fluke. Inouye (1903) collected 19 cases of brain infection. From 2 to 28, perhaps more, parasites occur in each patient.

Duration.—The longevity of the individual parasite is not established but cases are reported with histories extending over ten, twenty, and even thirty years; these are perhaps due to repeated infections.

[1] Synonyms.—*Distoma westermanii* Kerbert, 1878, originally from tigers; *D. ringeri* Cobbold, 1880, originally from man; *D. pulmonis; D. pulmonale; D. pulmonum; D. cerebrale.*

The species reported for hogs, cats and dogs in the United States is described as *P. kellicotti.*

In the lists of synonyms given in this paper, only the more common or the newer names are mentioned; for full lists of synonyms the reader is referred to the special literature on the various species.

Pathology.—(*a*) *Lung Infection.*—Occasionally deep, more commonly superficially in the lung, or directly under the pleura, are found roundish or flat cysts about as large as the end of the little finger, and containing from one to three parasites or in some cases only caseous contents. Katsurada (1900) is of the opinion that these cysts represent dilated bronchi, although he does not deny that cavities in the lung tissue may form independently of the bronchi; the lumen communicates with the neighboring bronchi by one large or numerous small openings and the different cysts may communicate with each other by means of direct or long irregular tubes; the septa between the tunnels may break down and a considerable cavity be thus formed (Manson); the wall of the cyst is rather stout, grayish-white, about 1 mm. thick; the inner surface is usually smooth, and the lumen may contain a reddish or brownish-green slimy fluid. When the worms settle in the bronchi, the walls undergo an inflammatory infiltration, a richly vascularized granulation with connective-tissue forms, and the original structure of the bronchi becomes lost. The bronchitis is caused not only by the worms but also by their eggs. An adhesive pleuritis may develop.

(*b*) *Brain Infection.*—Yamagiwa reports disseminated circumscribed foci of trematode eggs, usually also with giant cells, in the cortical substance of the brain; surrounded by connective tissue and round-cell infiltration; thickening of the wall of the bloodvessels, especially of the adventitia, and obliteration of some of the branches.

Symptoms.—These vary with the location and number of the parasites.

(*a*) *Lung Infection, Parasitic Hemoptysis.*—This is the usual and uncomplicated (primary) form and represents the typical paragonimiasis or pulmonary distomatosis as found in man. The onset may be so gradual that the beginning cannot be recognized with certainty. The only constant and specific characteristic is the presence of the eggs in the sputum; it is estimated that as many as 12,000 ova may be expectorated daily. The *sputum* is yellow to red or rusty brown, due to the presence of the microscopic eggs, and has a peculiar odor, partially due to blood; poor in water and rich in mucus, it varies from a small amount to 100 c.c. daily; blood is common but not constant, being present in points, strings, or larger amounts; while severe hemorrhages are not common, Baelz reports a case with a loss of a pound of blood within a few hours; intense anemia may result; the sputum is often discharged in spirals, resembling Curschmann's spirals, and contains eggs, blood, pus, mucus threads, alveolar and bronchial cells, numerous Charcot's crystals; Taylor and Mimachi each observed an expelled worm. There may be hoarseness or a chronic cough, usually light, rarely so severe as to disturb sleep and most urgent in the morning upon rising.

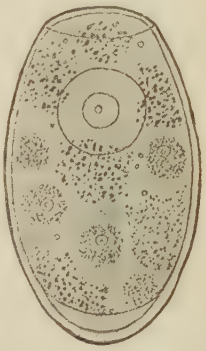
As the disease progresses the periods of cough and hemoptysis become more frequent and prolonged, tending more or less toward permanency and the amount of expectoration increases from a slight quantity at the onset to a much greater quantity later—as much as 350 c.c. in a few hours. All symptoms increase after physical exertion. Physical examination does not usually reveal anything abnormal except in severe cases; as the patient fails, auscultation shows diminished respiratory murmur,

the breath-sounds being vesicular but rarely weak, occasionally bronchial in character with dry or moist rales. Inouye reports unilateral or bilateral signs appreciable on percussion in 86 per cent. of 92 patients; only 1 of these had tuberculosis. The temperature is normal or but slightly elevated, even in severe cases. The patient may become exhausted by cough and hemorrhage; he also becomes deeply anemic, and suffers from dyspnœa on slight exertion. Slight œdema often occurs. After rest in bed all symptoms may abate except the cough and expectoration, and months may pass before a relapse occurs. Gradually the constitution becomes undermined, convalescence becomes less complete, periods of rest become shorter, those of prostration longer and more severe, œdema and anemia increase, and at last the exhausted patient dies.

The *lethality* of the uncomplicated form does not seem to be established, but it doubtless varies with the intensity of the infection.

(*b*) *Brain Infection.*—If the worms or their eggs gain access to the brain, a *cerebral distomatosis* develops, resulting in epileptiform attacks (Jacksonian or cortical epilepsy). It does not appear to be established in what percentage of cases this occurs, but it is an extremely serious and fatal form. The epileptic attacks may at first be a month or so apart, but they gradually increase in frequency and severity until death.

Fig. 59



Egg of lung-fluke showing ovic cell, yelk cells, and operculum. × 100. (Katsurada.)

(*c*) *Infection in Other Organs.*—Cysts of lung-flukes or their eggs may also occur in the eyelid, liver, mesentery, omentum, etc., but thus far such lesions do not appear to have the same importance as does the pulmonary or the cerebral infection.

Clinical Diagnosis.—The disease has been confused with tuberculosis, from which it may be readily distinguished by microscopic examination of the unstained sputum to find the characteristic egg. Diagnosis by roentgen-ray and by complement fixation has been reported.

Treatment.—No specific treatment is known. Inhalations have proved unsatisfactory. By sending the patient to an uninfected locality further infection is avoided, and with the lapse of time (the length of which is not known) the parasites may finally die and become disintegrated or be coughed up. Surgical interference has been suggested for cases in which the parasite can be definitely located.

Prevention.—(1) Destruction of infected sputum; destruction of cats and dogs showing the same disease; destruction of the infected lungs of swine. Thorough cooking of the food crustacea (crabs, crayfish), in or from infected localities.

Pulmonary Distomatosis Due to Fasciola gigantica.—One case of pulmonary distomatosis in man has been reported as due to *Fasciola gigantica*. This was doubtless a case of chance parasitism, as man is not known to be a normal host for *Fasciola*, and as the liver is the normal organ in which *Fasciola* occurs. The parasite is common in Africa in the

liver of buffalo, cattle, sheep, and goats; it was originally described for the giraffe; it is similar to *F. hepatica* in structure, but much narrower, measuring 25 to 75 mm. long by 3 to 12 mm. broad; eggs 145 to 190 by 75 to 90 μ. Snails (*Lymnaea natalensis* and *Physopsis africana*) are the reported intermediate hosts.

HEPATIC DISTOMATOSIS—LIVER-FLUKE DISEASE

At least eight different species of liver-flukes, representing four different genera (*Clonorchis, Opisthorchis, Dicrocoelium,* and *Fasciola*), have been found in connection with hepatic distomatosis of man. Infections with *Clonorchis* are common to man, dogs, cats and rats, and are much more frequent in man than are infections with *Dicrocoelium* and *Fasciola,* which man has in common with certain food animals, particularly cattle and sheep. Of the eight specific infections, one (an Asiatic disease) is much more important than all the rest combined.

Source of Infection.—For only three of these infections—namely, for the fascioliasis, due to *Fasciola hepatica;* clonorchiasis, due to *Clonorchis* and opisthorchiasis, due to *Opisthorchis felineus*—is the source of infection known (see pp. 511, 514, 517); for all of the others this is a matter of speculation, based upon analogy and circumstantial evidence. *Clonorchis* and *Opisthorchis* infections are contracted by eating undercooked or raw fish, *Fasciola* by eating plants on which the free swimming cercaria has encysted.

Clinical Diagnosis.—This is identical for all the infections. Make a microscopic examination of the unstained feces for eggs; also of the sputum and urine; the ova in pulmonary and venal distomatosis may be discharged per anum; hence, finding eggs in the feces, without excluding pulmonary and venal distomatosis, may lead to error. Unfertilized eggs of *Acaris lumbricoides* may be confused with eggs of *Fasciola,* but the latter are operculated, the former not.

Treatment.—There is no recognized specific treatment for any form of hepatic distomatosis, but recently published results with intravenous injection of tartar emetic give rise to hope of ultimate practical success. Remove the patient to a non-infected area, or, if he be kept at home, avoid further infection and give good, nourishing food.

Prevention.—The same general principles apply to all six infections.

CLONORCHIASIS

Asiatic Clonorchiasis or Japanese Liver-fluke Disease.—Geographical Distribution.—This infection is endemic in Asia, more especially in Japan and China, but is also found in the Philippines, India, Formosa, Mauritius, Annam, Tonkin and Korea. In the United States, a considerable number of cases have been found among Asiatics; numerous cases have been detected at the immigration stations and the infected persons have been returned to Asia.

Zoölogical Distribution.—So far as can be judged at present, man must be considered one of the normal hosts, but rats, cats, and dogs also appear to be normal hosts, and the infection occurs in swine.

The Parasite.—Asiatic liver-fluke disease is caused by elongate, lanceolate, non-spinose trematodes, belonging to the genus *Clonorchis*, characterized by the branched condition of the caudally located testes; the egg shell is dark brown, with sharply defined shoulder at the operculum, a fine reticulum on the egg shell (Fig. 60), and occasionally with a small knob at the posterior end. There is a slight difference of opinion whether all of these worms belong to a single species (*C. sinensis*) or to two distinct species (*C. sinensis* and *C. endemicus*); possibly they represent two geographic subspecies.

Fig. 60

Egg of Asiatic liver-fluke greatly enlarged, to show reticulum of egg-shell. (Stiles.)

C. sinensis, sensu str.,[1] is said to be found only in man; endemic in China and Japan, usually present in small numbers, less harmful, and measures 13 to 19 by 3 to 4 mm.; its eggs measure 26 to 30 μ by 15 to 17 μ.

C. endemicus[2] is reported for man, dogs, cats, and swine, from Japan, Tonkin, and Annam, is said to be present in larger numbers, and to be more harmful; it measures 6 to 13 by 1.8 to 2.6 mm., and its eggs are 26 by 13 to 16 μ. The adult worms inhabit particularly the gall-ducts, but may be found in the gall-bladder and in the pancreatic duct and (in the act of wandering) also in the duodenum and stomach. Katsurada (1900) found them in the pancreas in 9 out of 67 infections.

Source of Infection.—*Clonorchis* is contracted by eating raw or rare fish, and possibly also by drinking infected water; thirteen species of *Cyprinidae*, including *Carassius auratus* (gold fish), *Pseudorasbora parva*, *Leucogobia güntheri*, and several fishes belonging to other families are reported as harboring the encysted stage. The gold fish has been set loose in the streams of the United States, has reverted to an ancestral condition and is often sold here as "carp;" thus, at least one of the fish-hosts is wide-spread in this country. The reported molluscan hosts in Asia are *Bythinia striatula japonica*, *Melania hongkongensis*, and *M. libertina;* in the United States, *Bythinia tentaculata* has a wide distribution (New Hampshire to Michigan) and must be held under suspicion as potential intermediate host. Accordingly, the United States seem to present the host conditions necessary for the development of this disease.

Frequency.—According to Taylor, some native practitioners in the infected villages estimate that 1 in 7 or 1 in 5 of the population is infected, and where one member of a family is infected several members are likely to harbor the worm. Katsurada (1900) recognized 654 cases of infection in 1075 persons examined (60.8 per cent.) in three villages engaged chiefly in rice culture and in a region abounding in canals with dirty water.

[1] Synonyms.—*Distoma sinense* Cobbold, 1875; *Distomum spathulatum* Leuckart, 1876 (not Creplin); *D. spatulatum* Cobblod, 1879 (not Rudolphi, 1819); *D. hepatis innocuum; Opisthorchis sinensis* pars of authors; *Dicrocoelium sinense; C. sinensis major.*

[2] Synonyms.—*Distomum hepatis endemicum s. perniciosum* Baelz, 1883; *D. japonicum* R. Blanchard, 1886; *C. sinensis minor; C. sinensis* pars of authors.

It is said that in Japan, in certain regions where the water is poor, 20 per cent. of the inhabitants are infected, while in localities a few miles distant and with better water the parasite is comparatively rare. In some patients only a few parasites are present, while in others large numbers are found. Thus, Katsurada (1900) reports that of 72 cadavers examined, 4 contained from 2216 to 4361 worms each, and Blanchard (1901) reports 1 infection with over 10,000 parasites.

Duration.—Cases of infection of two to five years' standing seem to be common, but the longevity (apparently twenty years or more) of the individual parasites does not seem to be determined.

Pathology.—As the parasites are situated chiefly in the liver, this is the chief seat of the lesions; in fresh cases it is enlarged, sometimes hyperemic, in prolonged cases normal or decreased in size and more or less cirrhotic. The superficial gall ducts are prominent, white, opaque, and irregularly thickened; worms may be pressed out singly or in bunches in the thick, slimy, yellow to dark brown bile. The lesions are particularly of two kinds, involving the biliary canals and the hepatic parenchyma. When the worms enter the bile canals they obstruct the lumen more or less completely; the first result is bile stasis with resulting dilatation of the canals; the latter acquire considerable dimensions, while both epithelial and subepithelial layers undergo profound changes. Opinion has been expressed that these changes are due to mechanical causes; without doubt these are important, but the parasites seem to do damage other than by acting simply as foreign bodies, for in case of infection with *Fasciola hepatica*, Railliet has shown that the parasites suck blood from the capillaries in the walls of the canals. The lining of the ducts shows catarrhal irritation; the discharged mucus contributes to the occlusion of the canals; the glands undergo considerable hypertrophy which increases progressively and develops an extended adenoma; the newly formed bile canaliculi are numerous at the side of the chief canal with which they communicate; in sections nodules of several millimeters in thickness may be found which contain sections of a number of canals. The connective-tissue layer of the canals undergoes very active proliferation and may attain an enormous thickness, its outer layer showing more or less small-cell infiltration; it pushes before it the epithelium and thus contributes to the obliteration of the canal; it also compresses the hepatic tissue, at the expense of which it lodges and which then undergoes secondary lesions. A *cirrhosis* develops which, with time, acquires considerable proportions. The hepatic tissue undergoes granular and fatty degenerations and, little by little, atrophies. The lesions have a marked influence on the general nutrition; the arrest of bile causes digestive trouble; compression of the branches of the portal vein causes stasis toward its origin from which ascites results (Blanchard, 1901 c). The gall-bladder may be greatly enlarged. The spleen was enlarged in 6 of the 15 cases in which ascites was present, but in 1 case this organ was considerably reduced in size. Of 76 cases, 9 (11.8 per cent.) either showed or gave a history of icterus; of the 15 cases with ascites, icterus was present in 7 (46.6 per cent.) Concurrent hepatic cancer has been recorded.

Symptoms.—To a certain extent these depend upon the number of parasites present, so that light infections (carriers) may escape attention unless a microscopic examination is made. Usually there is at first increased, exceptionally decreased, appetite. In heavy infections, one of the first and most pronounced symptoms is enlargement and tenderness of the liver, preceded, attended, or followed by diarrhœa; the stools become irregular; the diarrhœa is at first irregular and intermittent, the attacks becoming more and more frequent and prolonged, until after two to five years there may be hardly any interval between them; the stools may be light, or dark and bloody, and may reach twelve per day; in some cases blood is present only at irregular intervals, in others the bloody diarrhœa becomes almost constant. The liver continues to increase in size, in some cases reaching the navel, though at times it apparently diminishes temporarily; there may be tenderness or more or less dull pain over the hepatic region and pressure may result in excruciating agony; jaundice, sometimes intermittent, is frequent; there is generally a dark, ashen discoloration of the skin. The temperature may be normal or increase to 100° F. After a time anasarca, likewise intermittent, appears and affects the legs especially. Night blindness is likely to occur. Epistaxis is rather common. Ascites often occurs, may increase for a time, then gradually diminish, to appear again and again. The patient is reduced by diarrhœa, becomes emaciated and grows anemic and weak, but the appetite is usually preserved. It frequently happens that the patient is reduced so low that life is despaired of, yet he may gradually and apparently become almost well (Taylor, 1884). Later, however, relapse occurs, and the same process is repeated again and again, ground being lost each time, until at length, worn out and exhausted, the patient dies after many years of illness.

Lethality.—Of 1495 cases, compiled for the province of Okayama, Katsurada (1900) reports 238 as fatal (16 per cent.); considering the number of carriers known to exist, the presumption is that this high death rate is based upon rather pronounced cases.

Clinical Diagnosis.—Microscopic examination of unstained feces to find the egg of the parasite is necessary. When in an infected locality a case of enlargement of the liver and bloody diarrhœa is seen, carefu examination of the feces usually shows the eggs.

Treatment.—No specific treatment is recognized, but Shattuck's (1923) results with intravenous injection of tartar emetic justify further study along this line. Whether any severe cases ever fully recover is not stated, but it seems *a priori*, that a change of locality to uninfected districts, thus preventing further infection, should be attended by at least a prolongation of life. Katsurada (1900) suggests the advisability of laparotomy in some cases, in order to press the parasites out of the gall ducts into the intestines.

Prevention.—(1) Destruction of all cats and dogs affected with the parasites, and proper disposal of all feces from infected persons. (2) Avoid eating raw or undercooked fish.

OPISTHORCHIASIS

The term opisthorchiasis was introduced by Looss (1905) to designate infection with flukes belonging to the genus *Opisthorchis*, a group characterized chiefly by the position of the unbranched testes near the caudal end of the body. In man we may distinguish at present two distinct infections by species of this genus; in order of known importance these are the European and the Indian species.

Siberian Opisthorchiasis or Siberian Liver-fluke Disease.—Geographical Distribution.—The parasite is reported for cats and dogs in France, Germany, Holland, Italy and Russia; cases in man are reported for Prussia and Siberia. The report of this parasite in the United States is based upon a misdetermination (*Opisthorchis pseudofelineus*).

Zoölogical Distribution.—The cat, and possibly the dog, the fox (*Vulpes vulpes*), and the glutton (*Gulo borealis*) form the natural hosts for this infection; it is not yet thoroughly established whether man is a natural or a chance host, though indications point to the latter.

The Parasite.—This infection is caused by the European cat-fluke (*Opisthorchis felineus*), a lanceolate, non-spinose worm, measuring from 8 to 15, rarely to 18 mm. long by 1.25 to 2.5 mm. broad; the testes are lobate, but not branched; eggs oval, yellow brown, 26 to 30 by 11 to 15 μ, one side slightly flatter than the other; with sharply defined operculum on the more acute pole and containing a ciliated miracidium at oviposition. The adult parasites inhabit the gall ducts, but are occasionally found in the pancreas and duodenum.

Source of Infection.—The embryo does not hatch in water, but it hatches in snails belonging to the genus *Lymnaea*, although it does not develop further in this host; *Dreissena polymorpha* also has fallen under suspicion. Askanazy (1906) has traced the infection to the dace (*Leuciscus rutilus*) and the ide or orf (*Idus idus* (s. *melanotus*); in Roumania, another fish, *Tinca tinca*, harbors the encysted cercaria.

Frequency.—This is an exceedingly common parasite of cats in some parts of Europe. Winogradoff (1892) reported 8 cases of infection (6.45 per cent.) in man in 124 autopsies at Tomsk, Siberia; Rindfleisch (1910) reported 40 cases, during nine years, in the Königsberg clinic; and Kurimoto (1900) and Kholodovsky are authority for 1 case in St. Petersburg, Russia, in a patient who had been in Siberia; infection in man is recorded for Tonkin, also. In the cases reported for man, there were several to a thousand (Askanazy, 1901) parasites present.

Wingogradoff reported an additional case of infection with a small spinose fluke which he supposed was a young *O. felineus;* but Braun has suggested that this might be *Pseudamphistomum truncatum*, a small spinose fluke which occurs in the dog, cat, fox, glutton and seal.

Pathology.—In general this is similar to that of Asiatic clonorchiasis, except that no such severe infection has been studied. Askanazy (1900 *b*) summarizes the pathology as cholangitis catarrhalis and pericholangitis fibrosa or as Virchow described it in fascioliasis, as a chronic choleportitis and fibrous periportitis. Bossuat (1902) summarizes the condition as an irritation of the walls of the biliary canals, a thickening with pisiform

dilatations, followed by a veritable cirrhosis. Concurrent hepatic cancer has been recorded.

Duration.—Unknown. In 1 case probably nearly three years.

Symptoms.—The cases have not all been carefully studied clinically. In general, approximately the same clinical picture may be expected which is found in corresponding infections with the Asiatic fluke, for the worms are very closely related and the lesions more or less the same. According to Askanazy (1900 *b*), Winogradoff reported icterus in 5 of his cases, decreased liver in 5 cases, enlarged liver in 2 cases, ascites in 3 cases.

Lethality.—In none of the cases reported is the parasite given as the direct cause of death.

Clinical Diagnosis and Treatment.—See p. 513.

Prevention.—In view of the fact that fishes form the intermediate host, it will be well to avoid eating raw fish.

Indian Opisthorchiasis or Indian Liver-fluke Disease.—Geographical Distribution.—Thus far reported only for Calcutta, India, unless Winogradoff's ninth case (which Braun thinks may perhaps have been due to *Pseudamphistomum truncatum*) belongs here (?).

Zoölogical Distribution.—Man and dogs. It is not yet known whether these are normal or merely chance hosts. The view that this parasite occurs in the North American red fox (*Canis fulvus*) is based upon an error of identification.

The Parasite.—The Indian liver-fluke, *Opisthorchis noverca* Braun, 1903, is a lanceolate, spinose fluke, 9 to 12.5 mm. long by 2.5 mm. broad, which lives in the gall ducts. Eggs oval, 34 by 19 to 21 μ.

Symptoms.—In general, these are probably the same as for other species of this genus, see p. 513.

Source of Infection, Duration, Lethality, and Prevention.—Unknown.

Frequency.—Only 2 cases (McConnell, 1876 and 1878) known.

Siam Opisthorchiasis.—In Siam, *Opisthorchis viverrini* Poiriei, 1886, has been reported twice at autopsy, of man, in the liver and intestine; the egg is reported in the stools of 15 per cent. of the prisoners in Chiengmai, Siam. Infection probably occurs through eating fish.

Philippine Opisthorchiasis.—*Opisthorchis* (s. *Paropisthorchis*) *caninus* Barker, 1911, has been reported for the Philippines and India.

LANCET FLUKE INFECTION

Geographical Distribution.—This infection seems to be primarily one of Continental Europe. Its exact distribution cannot be stated, as there has been considerable confusion in the determinations of infections with this and other lanceolate parasites. Aside from Europe, it is reported for Northern Africa, Siberia, Turkestan, and North and South America.

Zoölogical Distribution.—The same confusion also exists in reference to the hosts. Apparently cattle and sheep are the normal hosts for this worm, which is also reported for the goat, deer (Hirsch), horse, ass, hog, hare, rabbit, and man. Certainly many and possibly all of the reported occurrences of this infection in carnivorous animals (dogs and cats) are based upon confusion with *Opisthorchis*, see p. 514.

The Parasite.—The lancet fluke (*Dicrocoelium lanceatum*[1] Stiles and Hassall, 1896) is a non-spinose, lanceolate trematode, 4 to 9 mm. long by 2 to 2.4 mm. broad, characterized by the anterior position of the testes, which are between the acetabulum and the ovary, and by the posterior position of the uterus. Eggs, dark brown, thick-shelled, 38 to 45 by 20 to 30 μ, with a distinct operculum and containing a ciliated miracidium when oviposited; the embryo is provided with two dark spots in the posterior portion.

Source of Infection.—Unknown. Embryos hatch in the intestine of slugs (Arionidæ) but not in water; they do not, however, develop further in these mollusks; *Planorbis marginatus* and *P. umbilicatus*, also, have fallen under suspicion as possible intermediate hosts.

Frequency.—While the parasite is quite common in cattle and sheep, only about 7 cases of its occurrence in man have been reported. It is doubtless purely an accidental parasite for man.

Duration.—Unknown.

Symptoms, Lethality and Pathology.—Probably not serious, as only light infections are likely to occur in man. Kirchner reports 1 case with gall stones. It seems not impossible that Mehlis' case, in which a woman vomited 50 specimens of this parasite and 9 of *Fasciola hepatica*, resulted from eating infected liver which was not thoroughly cooked.

Clinical Diagnosis and Treatment.—See p. 513.

FASCIOLIASIS—INFECTION WITH FASCIOLA

Fascioliasis is, properly speaking, distomatosis caused by species of the genus *Fasciola*. While the liver is the normal habitat for these worms, fascioles occasionally infect other parts of the body. In man fascioliasis is probably always due either (1) to a purely chance infection by the larvæ which then develop in the liver, or, in rare cases, some other part of the body, as the lungs (p. 509), the eye (p. 530), or the veins (*Hexathyridium venarum*), etc.; or (2) to accidental infection with the adult worm, due, as Khouri (1904) has shown, to eating raw liver containing these parasites.

Geographical Distribution.—The common liver-fluke is reported with a very wide distribution, but as the parasites on different continents are studied more carefully it is found that the infections alleged to be due to this species are specifically distinct, although generically identical. On account of these changes in ideas regarding classification this entire subject should be restudied. Europe is the type locality of *Fasciola hepatica*, and the same parasite seems to occur in North America and Australia. It is reported also for Asia, Africa, and South America.

Zoölogical Distribution.—This infection is reported from some animals which are probably not actually infected with it, but its normal hosts seem to be cattle, goats, and sheep.

The Parasite.—*Fasciola hepatica*[2] Linnaeus, 1758, is a flat, leaf-like, spinose worm measuring 18 to 30 mm. (reported to 51 mm.) long by

[1] A synonym of *D. dendriticum*, according to Odhner.

[2] Synonyms,—*Distoma hepaticum; Fasciola humana; Hexathyridium venarum*,

13 mm. broad; the intestine, testes, ovary, and vitellogene glands are profusely branched. Eggs, yellow-brown, oval, 130 to 145 by 70 to 90 μ, with distinct operculum, not containing embryo when oviposited.

Source of Infection.—Various snails, belonging to the genera *Ampullaria*, *Helix*, *Lymnaea*, and *Physa*, have been reported as intermediate hosts; *Lymnaea* is usually accepted as the most important. Infection of man, sheep, etc., takes place normally by swallowing the cercaria which encysts on plants in marshes.

Frequency.—While this infection is rather common in cattle and sheep, especially those pasturing in marshy districts, it seems to be purely accidental in man. Not every case reported as *Fasciola hepatica* is to be accepted as such. One source of error is to mistake single segments of tapeworms for liver-flukes; the writer has seen several cases in which this had been done. Blanchard carefully collated the authentic cases reported for man and Moniez added several to Blanchard's list. One case for Porto Rico is known to the writer; but while the parasite is a *Fasciola*, it may possibly represent a new species. Cases of infection have been reported for the blood and in subcutaneous tumors.

Attention may be directed to the fact that the eating of raw liver infected with *F. hepatica* may be a much more serious matter than has generally been supposed and may cause in man a condition which, in certain localities at least, is apparently more common than is the presence of the common live-fluke in the human liver.

Halzoun.—According to Khouri (1904) there exists in northern Liban, Syria, a disease known as "halzoun,"[1] which he attributes to *Fasciola hepatica* contracted through eating raw goat-liver infested with the parasite. His experiments upon rabbits, as well as clinical observations, indicate that the parasites attach themselves to the pharyngeal mucosa where they gorge themselves with blood; Khouri thinks that the parasites may secrete a substance which acts as a vasodilator. After gorging themselves with blood the flukes loosen their hold, reach the stomach, or are expelled with the vomit. There are two sets of symptoms: namely, congestive (a more or less intense œdematous congestion of the buccopharyngeal mucosa, of the larynx, nasal fossæ, tonsils, Eustachian tube, ear, conjunctivæ, and lips) and mechanical (dyspnœa, dysphagia, aphonia) resulting from the first phenomena.

Symptoms.—After eating the infected raw liver, the patient experiences an itching sensation deep in his throat; soon he feels more or less malaise; the itching increases, extending to the ears and becoming painful; a buzzing in the ears follows and a sensation of auricular tension exasperates the patient. Two or three hours after onset the itching lessens; swallowing becomes difficult and painful; dysphonia develops and may extend to complete aphonia. The most alarming symptom is the dyspnœa, varying to orthopnœa in severe cases or asphyxia in fatal cases. The aspect is typical; the face is congested, the lips thick, cyanotic, and livid; an abundant saliva flows; the eyes are highly congested and there may be lacrimation; the conjunctivæ are injected and œdematous;

[1] Arabian word for spiral or snail.

photophobia and exophthalmia are common; the sight remains normal. In severe cases the neck is swollen and œdematous; palpation shows a variable submaxillary and cervical adenopathy and a diffuse puffiness; the œdema invades the cervical cellular tissue, in serious cases extending to the clavicle. Examination of the throat shows congestion and a more or less intense œdema of the pharyngeal mucosa of the palate and especially of the uvula and tonsils; the latter are considerably enlarged and, in severe cases, may meet in the median line, leading to asphyxia. Laryngoscopic examination shows an unusually narrowed superior larynx, of red-violet color, the vocal cords are slightly œdematous, but the opening of the glottis is not seriously restricted. There is rather an intense reddening of the external auditory canal and especially of the tympanum.

The temperature usually remains normal but the pulse increases with the dyspnœa. Examination of the lungs and urine is negative.

In the light cases, dysphonia and distinct dyspnœa are not observed; the duration is short, varying from a few hours to two or three days. In the grave form the symptoms reach their maximum; the incubation is only five to twenty-five minutes; after ten to eighteen hours, the pharyngolaryngeal symptoms are intense; usually the attacks lasts five to eight days; if the symptoms do not ameliorate by the end of thirty-six hours, to continue for four to five days in benign form, death is reported as inevitable.

Complications.—As complications may be found: abscess, especially in the external auditory canal and in the mastoid region, suppurative otitis media, followed by perforation of the tympanum, and peripheral facial paralysis which disappears after eight or ten days.

Duration.—Attacks vary in length from a few hours to ten days. Most patients recover, death being exceptional.

Diagnosis.—As a rule this is not difficult but some cases may be confused temporarily with diphtheria, œdema of the glottis, cardiac or pulmonary dyspnœa, and acute iodism.

Treatment.—Vomiting dislodges and expels the parasite, and should be encouraged; it is more effective if the stomach is well filled.

Prevention.—Avoid eating raw liver.

INTESTINAL DISTOMATOSIS

The entire subject of intestinal distomatosis in man needs a careful restudy. Undoubtedly the infectious are much more common than is ordinarily assumed, but we cannot as yet say for which infections man forms a normal and for which an accidental host.

Geographical Distribution.—So far as the writer has records, intestinal distomatosis in man is reported chiefly of Asiatic and African origin.

Zoölogical Distribution.—Similar infections, some of them generically, and a few of them specifically, identical with those found in man, are exceedingly common in other animals.

The Parasites.—Intestinal distomatosis in man may be caused by the following flukes:

Fasciolopsis buskii (Lankester, 1857).—This is the largest and the most important of the intestinal flukes of man; thus far cases are known only of Asiatic origin (India, Assam, Siam, China, Straits Settlements, Sumatra), but Moore and Terril (1905) reported 1 imported case in the United States, and Nicoll (1910) reported a case for Natal. The worm measures 27 to 37 mm. (or even 75 mm., after Busk) long by 5.5 to 12 or 14 mm. broad, and 1.5 to 2 mm. thick. While not unlike the common liver-fluke (*Fasciola hepatica*) in superficial appearance, it can be easily distinguished from that form by its very large acetabulum and by its simple intestine. The eggs measure 120 to 130 by 77 to 80 μ with very delicate operculum.

The life cycle was discovered by Nakagawa (1921): the eggs (in water) hatch out an embryo (miracidium) in two to three weeks (in summer); this bores into certain fresh water snails (*Planorbis coenosus, Segmentina largillierti*) and transforms to a sporocyst in which redia develop by the seventh day; in fourteen days the rediæ reach the snails' liver and each one develops 4 to 7 cercariæ (in some cases, daughter rediæ develop) by the thirty-fifth day; the cercariæ escape into the water, from the snail, and by the thirty-eighth day may encyst on aquatic plants which (as food) then carry the infection to man, hogs, or dogs; fresh water snails and fishes also are said occasionally to contain the encysted, infective, stage. Eggs were found on the ninety-third day in the feces of an experimental infection in a pig.

This parasite, long assumed to be rare, has been shown by Barlow and others to be exceedingly common in man in some localities and to be of serious clinical and economic importance. The more severe cases of the disease have been divided into three stages: (1) A slight anemia with weakness; (2) diarrhœa with abdominal pains, profound anemia, enlarged abdomen; (3) œdema, extreme anemia, ascites; death.

Treatment.—Thymol, or calomel, or beta-naphthol.

Several other species of *Fasciolopsis* (*F. fülleborni* in Calcutta and Egypt; *F. goddardi* and *F. spinifera* in China; *F. rathouisi* in Asia) have been reported as intestinal parasites of man, but there is a tendency to view these as synonyms of *F. buski.*

Far less important than *Fasciolopsis* are the following intestinal flukes reported for man:

Echinostoma (s. *Fasciolella*) *ilocanum* (Garrison, 1908), in the Philippines; development unknown; treatment thymol.

E. malayanum Leiper, 1911, in Malay States; development unknown.

Euparyphium jassyense Leon and Ciurea, 1922, in Roumania; development unknown.

Artyfechinostomum sufrartyfex Lane, 1915, in India; development unknown. Possibly a synonym of *E. malayanum.*

Echinochasmus perfoliatus japonicus Tanabe, in Japan, cercaria reported for *Bythinia striatula japonica;* the encysted metacercaria for fresh water fish.

Heterophyes heterophyes Sieb., 1852, Egypt and Orient; encysted stage reported for a mullet, *Mugil cephalus.*

H. nocens Onji, 1915, Japan; very common; encysted stage reported for Japanese mullet, *Mugil japonicus.*

Metagonimus yokogawai Katsurada, 1913 (syn. ? *ovatus* 1913, ? *Loxotrema ovatum* 1908), in Japan and Formosa; cercaria reported for various snails (*Blanfordia* seu *Katayama nosophora, Melania ebenina, M. extensa, M. gottschei, M. libertina, M. nodiperda quinaria, M. obliquegranosa,* and *Pyradus cingulatus);* encysted metacercaria (infecting stage) reported for gold fish (*Carassius auratus*) and other fishes (*Plecoglossus altivelis, Leuciscus hacuensis, Cyprinus,* etc.).

Stamnosoma armatum Tanabe, 1922, in Japan, encysted stage reported for cyprinoid fish.

Stamnosoma formosanum Nishigori, 1924, in Formosa, encysted stage in various fishes.

Gastrodiscus s. l. (or *Gastrodiscoides* s. str.) *hominis* Lewis and McCon., 1876, in India, Assam, Malay States; life history unknown.

Watsonius s. str. (or *Pseudodiscus* s. l.) *watsoni* (Conyngham, 1904); Africa; life history unknown.

BLOOD DISTOMATOSIS—BILHARZIOSIS[1]—BLOOD-FLUKE INFECTION

Geographical Distribution.—Probably rather generally as a tropical and subtropical disease. Occasional cases, chiefly imported, are recorded for the temperate climates; imported cases have been recognized in the United States.

Zoölogical Distribution.—Blood-fluke infection, due to several different genera of worms, is reported for mammals, birds, and turtles. Infections generically (*Schistosoma*) identical with those of man are known for various mammals (cattle, horses, etc.). Infections specifically identical with human blood-flukes are reported either in various mammals in Nature (*haematobium* for *Cercocebus fuliginosus; japonicum* for cattle, horses, sheep, goats, cats, dogs, pigs) or in laboratory experiments (monkeys, guinea-pigs, mice, rats, rabbits). Two species of blood-flukes of cattle (*S. bovis, S. spindalis*) are reported, somewhat doubtfully, for man.

Of the trematodes of man, the schistosomes are the only ones which are not hermaphroditic, and which have non-operculated eggs.

So far as the life cycles have been demonstrated, all schistosomes require a snail as intermediate host and the forked tailed, apharyngeal, blind, cercariæ infect their final mammalian hosts percutaneously when the mammals are in water.

The Parasites.—Bilharziosis in man is due to at least three species of *Schistosoma* (*haematobium* in the veins, in vesicle bilharziosis; *mansoni* in veins, *japonicum* in veins and arteries, in intestinal bilharziosis); possibly also, exceptionally, two additional species (*bovis* and *spindalis* of cattle) may infect man.

The African blood-fluke, *Schistosoma haematobium*[2] (Bilharz, 1852),

[1] Synonyms.—Egyptian hematuria; endemic hematuria; bilharzian hematuria; bilharzia disease.

[2] Synonyms.—*Distomum haematobium* Bilharz, 1852; *Bilharzia haematobia* (Bilharz) Cobbold, 1859; *Bilharzia capensis* Harley, 1864.

occurs chiefly in Africa and adjacent islands but extends to Portugal, Greece, Asia, and Australia and is occasionally found elsewhere; imported cases have been found in the United States. The male is 4 to 15 mm. long by 1 mm. broad; the sides are curved ventrally to form the gynecophoric canal; the worm is armed with numerous spinose warts; it has 4 or 5 testicles and its ceca unite far caudad. The female is filiform, 15 to 20 mm. long and lives in the gynecophoric canal of the male; its vitellaria occupy the caudal fourth of the body and its long uterus usually contains several mature oval eggs which measure 135 to 160 μ long by 55 to 66 μ broad, and are provided with a terminal spine. It has been reported once in Nature for a monkey (*Cercocebus fuliginosus*) and experimentally for monkeys, guinea-pigs, rabbits, rats, and mice. The nomenclature of some of the intermediate snail hosts is *sub judice*, but they are assigned to the genera *Bulinus* (*africanus, contortus, dybowski* s. *Physa alexandrina, forskali, innesi*, in Africa), *Isidora* (species, in Africa), *Lymnaea* (*natalensis*, in Africa), *Physopsis* (*africana*, in Africa), and *Planorbis* (*boissyi, corneus, dufourii, metidjensis*, in Portugal).

Manson's blood-fluke, *Schistosoma mansoni*[1] Sambon, 1907, is reported for Africa, West Indies, Panama, South America (Brazil, Colombia, Dutch Guiana, Peru, Venezuela). The adult is very similar to *S. haematobium*, with which it was long confused, but the eggs have a subterminal (lateral), instead of a terminal, spine. The male has 8 testicles; the caudally united cecum is longer than in *S. haematobium*. The vitellaria of the female are in the caudal two-thirds of the worm, the uterus is relatively short and contains only one ripe egg at a time. The snail hosts are assigned to the genera *Ampullaria* (*luteostoma*), *Physopsis* (*africana*, in Egypt), and *Planorbis* (*boissyi*, in N. Africa; *culturtus; centimetralis, olivaceus*, in Brazil; *guadelupensis*, in Venezuela; *pfeifferi*, in S. Africa).

The Asiatic blood-fluke, *Schistosoma japonicum*[2] (Katsurada, 1904) is endemic in Japan, China, and Formosa; cases have been reported also for the Philippines, S. Africa, and (imported cases) the United States. The male measures 7 to 12 mm. long by 0.53 mm. to 0.8 mm. broad; it is not armed with spinose warts; gyncophoric canal present. The female measures 8 to 12 mm. long. The eggs, 60 to 90 by 30 to 50 μ, are not provided with the sharp terminal or subterminal spine; near one pole, however, they show a small knob. *S. japonicum* presents more serious features from the point of view of eradication than does either *S. haematobium* or *S. mansoni*, for it is reported as a parasite not only of man but also of various domesticated animals (*Bos sinicus*, cats, dogs, swine, horses, sheep, and goats); it is experimentally communicable to monkeys guinea-pigs, rabbits, rats, and swine. The intermediate hosts (snails) thus far established belong to two genera: *Katayama* (*formosana*, in Formosa; *nosophora nosophora* and *n. yoshidai* in Japan; *fausti* and *f. cantoni*, in China) and *Oncomelania* (*hupensis*, in China).

The young blood-flukes live in the veins of the liver; in the portal vein there are but few young pairs; the gravid worms wander to the blood-vessels of the intestine and bladder wall. Oviposition begins while the

[1] Synonym.—*Schistosomum americanum* da Silva, 1909, in Brazil.
[2] Synonym.—*Schistosoma cattoi* Blanchard, 1905.

parasites wander from the portal vein to the pelvis, and eggs are deposited in various organs. The terminal spined eggs (*haematobium*) are found in the urine; the eggs with lateral spine (*mansoni*) are especially common in the liver and intestine and are discharged in the feces, but they are occasionally reported for the urine; the knobbed eggs (*japonicum*) are found in the feces. The ova (80 by 30 μ in utero) increase in size as they work through the tissues into the lumen of the intestine or of the bladder; during this process they develop a ciliated embryo so that the miracidium is present when the egg is voided by the patient.

Source of Infection.—The life cycles of all three species are similar in general, but differ in some details. The embryonated eggs may hatch in the intestine (*mansoni, japonicum*) if the diarrhœa is severe, but usually the ova escape from the host with the urine (*haematobium*, exceptionally *mansoni*) or feces (*mansoni, japonicum*); the egg of *S. japonicum* remains viable in water about ten days; the ova of all three species hatch in water (*mansoni* in a few minutes at 30° C.); the cercariæ break through the side of the egg usually near the head (*haematobium*) or through a transverse slit (*mansoni*), under conditions favorable as to temperature and light; they swim around in the water, seeking the proper snail host, *S. mansoni* swimming toward the light; if unsuccessful in this search, they die in about twenty-four hours (*haematobium, mansoni*); if successful they penetrate the snails' skin (*mansoni*, the feelers, ten to fifteen minutes; *japonicum*, the head or foot), and develop into a sporocyst (*mansoni* in three to four days) which form (*japonicum*, about 50 cylindrical) daughter sporocysts by budding (*mansoni* on fifth to sixth day); the latter (*mansoni* about twentieth day) migrate to the hepato-pancreas, and (*haematobium*) form tubular branches; the cercariæ develop in the daughter sporocysts (*mansoni*, about thirtieth day). The entire cycle (*japonicum*) in the snail lasts about three weeks and all cercariæ from one cyst are of the same sex, either male or female. The development of *S. mansoni* is reported as incomplete if the worm enters *Ampullaria, Lymnaea*, or *Physa*, but complete in *Planorbis*. Under proper influence of sun (*mansoni*) and heat, the cercariæ escape from the snail (*mansoni*, during the next two to three months), and swim in the water seeking their mammalian host (*haematobium* swims at the surface; *japonicum* shuns the light, dies at temperatures below 2° C. and above 50 °C.); upon penetrating the skin (*haematobium* in ten minutes; *japonicum*, at 20° C. and above) the cercariæ lose their tail, enter the veins (*japonicum*, on third day, in portal system), and become adult (*haematobium*, in about two months; *mansoni* oviposits in five weeks and in experimentally infected rabbits and guinea-pigs eggs have been found in the feces ten weeks after percutaneous infection; *japonicum* copulates about twentieth day, oviposits about third week). Experimental infection per mouth has been obtained with *S. haematobium*, but it is probable that the cercariæ immediately traversed the buccal membrane into the veins.

The immature stages or young adults correspond to the *toxic* stage of disease. The females lie in the ventral gynecophoric canal of the males, but (especially *haematobium*) the majority of the females desert the males before migrating to the bladder (*haematobium*), vagina (*haematobium*),

rectum (*mansoni*, *japonicum*, *haematobium*), or elsewhere. Upon reaching the smaller veins or even entering the tissues, the worms oviposit. Many of the eggs remain in the tissues, others escape into the lumen of the bladder, vagina, or rectum.

Frequency.—Bilharziosis naturally varies in frequency according to liability of coming in contact with infected water. Accordingly, in some localities it represents an occupational disease, and any sex distribution observed will be expressed according to the occupation. Thus in Portugal it is found more among washerwomen; in Asia it is much more common in males than in females and in rural districts than in cities. In a school near Cairo, Kautsby Bey found 98 cases in 124 boys examined, or nearly 80 per cent.; in two city schools, Engel Bey found 61 children, or 30.5 per cent. infected in 200 examined (Looss, 1905). Its lesser frequency in later than younger years is explained at least in part, according to various authors, by an acquired immunity, but it is admitted that the cercariæ attack persons of all ages. *S. japonicum* is reported in the new-born, when the mother, during pregnancy, had been exposed to infection; it is reported also for the fetuses of dogs and guinea-pigs. Accordingly, congenital infection is possible. Postmortem statistics indicate that it is present in quite one-half of the population of Egypt (Manson), and it is even more common in Uganda (Low). Several to 40 (Sonsino) or even to 300 (Kartulis) worms may be found in one patient. Ruffer (1910) reports the eggs from the kidneys of 2 out of 6 Egyptian mummies dating from 1250 to 1000 B.C.

Duration.—The incubation of the disease is about four to five months (Brock *et al.*), and it is said to last usually about two years (Milton, 1902); cases of longer duration are recorded in patients who have passed ova for nine (Sonsino) to fifteen years (*haematobium*) or seventeen years (*mansoni*) after leaving the infected area, and some authors refer to cases of twenty to thirty years standing; evidence is not presented that these were not due to repeated infection.

Pathology.—It is generally admitted that it is the eggs rather than the worms that are of the greater importance. These ova work their way into and through the tissues, particularly in the walls of the bladder, rectum, and vagina; they may also be found in the brain, liver, lungs, heart, spleen, pancreas, kidneys, omentum, peritoneum, appendix, ligaments of the uterus, in gall stones, and in the cutaneous epithelium. At first the eggs lie in the blood capillaries, but leaving these they collect in groups in the tissue, the infiltrated places appearing as yellowish to whitish specks, and as the lesion increases it forms a papular elevation containing eggs and minute dilated bloodvessels. These thickenings increase in size and may coalesce until the entire mucous membrane of the bladder becomes involved. Round, slightly projecting, dense patches of inflammatory thickenings, with granular surface and of hard consistency are seen, especially in the trigonum. After a certain age the patches begin to break down, and even slough, giving rise to ulcers, and crevices on their surfaces, which tend to retain a certain amount of urine and favor deposition of its salts. In some cases the increase in the mucous membrane seems to be out of all proportion to the development of fibrous

tissue and, in these cases, polypoid excrescences, sometimes ulcerated, may protrude into the lumen and may contain the worms as well as their ova. The bilharzia growths may cause retention of urine, resulting in dilatation of the ureters and disease of the kidneys. The muscularis hypertrophies. The capacity of the bladder is decreased and its mucosa becomes covered with a bloody mucus containing numerous eggs. Carcinoma may develop.

Lesions similar to those of the bladder may be found also on the prostate, in the ureters (especially the lower third), less frequently in the pelvis of the kidney. The ureters may present constrictions and spindle-shaped or sacculated dilatations. Pyelitis, hydronephrosis, abscess, etc., may follow, and calculi (more important in the early stages of the disease) may form in the bladder, ureters, or kidneys. The vesiculæ seminales, vagina, and cervix may also show a hyperplasia with a bloody discharge containing fluke eggs. There is some variation in pathology, according to the species of parasite. Thus, endophlebitis occurs in infections with *mansoni* and *japonicum*, but is denied in *haematobium* cases.

In *mansoni* infestations, irritation by the eggs in the wall of the rectum results in soft or friable polyps; an ex-ulceration occurs, contrasting with the undermined ulcer of amœbic dysentery; the submucosa becomes inflamed, contains numerous eggs, and forms the axis of the polyps, with endophlebitis. In general, the parasites and their eggs cause a thickening of the intestinal wall which becomes more or less sclerosed. In this infection, more than in vesical bilharziosis, the females may scatter and lay their eggs in the liver, lungs, etc. The ova may cause a reaction in the hepatic tissues, resulting in nodules with a central egg. In advanced cases, blood examination may reveal a light anemia and a slight eosinophilia. Infestations with *japonicum* cause lesions especially in the liver, spleen, intestine, and peritoneum. In the invasion stage, the skin usually shows red points, papules, or pustules; there may be a slight œdema and minute hemorrhages. The hepatic capsule may become quite thickened; the hepatic tissue may show more or less sclerosed parasitic nodules; an extensive periportal cirrhosis may develop; the large portal veins may exhibit endophlebitis; the liver may increase or decrease in size. The spleen may enlarge. The intestinal lesions are of relatively secondary importance; at places, the glandular layer may be destroyed, or cysts may form; in the submucosa, endophlebitis appears to be absent; fibro-adenomata are rare. The peritoneum contains numerous eggs, and on autopsy may exhibit signs of a chronic peritonitis with ascites. The blood may show 14 to 50 per cent. of eosinophiles.

Symptoms.—*Forms.*—Various forms of bilharziosis have been described, as cutaneous (initial), vesical, vaginal, intestinal, hepatic, splenic, cerebral, febril, and latent. As each female blood-fluke does not produce many eggs, it requires quite a heavy infestation to cause serious symptoms and the number of carriers may be far in excess of the patients. This appears to obtain especially for *S. mansoni* which contains only one mature egg at a time. In cases of heavy infestations, blood-flukes may manifest two, three, or four rather distinct clinical stages, namely: (1) a *cutaneous* stage, due to the penetration of the cercariæ, (2) a *toxic* stage, apparently

due to the developing flukes, (3) a *latent* stage of seeming recovery, and (4) *traumatic* stage, due to the gravid females and the eggs they produce.

1. *Cutaneous Stage of Invasion.*—The penetration by *S. mansoni* causes a more or less pronounced itching; that by *S. japonicum*, a rather intense pruritus followed by skin lesions known locally as "kabure."

2. *Toxic Stage.*—About four to six weeks after infestation, by *S. haematobium*, the patient experiences fever, chills, sweats, lassitude, urticaria, and œdema. *S. mansoni* patients exhibit fever, abdominal pain, tenderness and congestion of the liver and spleen, urticaria, bronchitis, diarrhœa and marked eosinophilia (36 to 76 per cent.). *S. japonicum* cases show a febrile condition (generally intermittent and with sweats as in malaria) lasting three to six weeks,with œdema, urticaria, epigastric pains, diarrhœa or constipation, some mental depression, and an eosinophilia of 14 to 60 per cent.

3. *Latent Stage.*—In *S. haematobium* infestations, the patient may lose weight for several weeks and then appear as if recovered.

4. *Traumatic Stage.*—This represents the condition usually recognized as the typical, more or less chronic, picture of bilharziosis.

In *vesical* bilharziosis (*haematobium* infestations), the ova are confined chiefly to the urogenital system and the prominent symptoms are hematuria, pains in the lumbar region, left iliac fossa, thigh, or vulva, either spontaneous or on micturition; cystitis, calculus, urinary fistulæ, vaginal tumors, and nephritis may develop. The course is rarely acute (Greisinger); it usually stretches over years and if death occurs, it is, as a rule, from some intercurrent disease; Ruffer isolated the colon bacillus in the kidney of all the fatal cases he observed (Innes).

Hematuria is the most prominent feature. In many cases the patient suffers little or no inconvenience. The simple hematuria occurs chiefly in the better classes, the severer forms of bilharziosis occurring among persons who are subject to long and severe physical labor and almost exclusively among men. At the end of micturition a few drops of more or less pure blood are expelled and this may be the only symptom observed; the amount of blood lost is usually small, but in some cases more extensive; it may clot in the bladder and cause acute retention. Later, vague pains in the perineum, lumbar region, over the pubes, and a burning sensation in the urethra during micturition are experienced. At first the frequency of urination is not increased. All symptoms increase temporarily after excesses in diet or exercise, or during straining in defecation. The sediment of the urine contains blood and epithelial cells, mucus, and blood-fluke eggs.

The simple hematuria may be followed by *vesical catarrh*, increased micturition with severe pain and tenesmus, later by pronounced *cystitis*. The urine gradually becomes bloody, cloudy, and offensive; loosened tissue from the bladder may clog the urethra; residual urine becomes constant; pyelonephritis and septic cystitis may result. Relatively soft vesical *calculi* may form and in infected geographical areas patients with vesical calculi commonly give a history of hematuria. Calculi may form in the kidneys or ureters and cause hydronephrosis. Hypertrophy, contraction or dilatation of the bladder may occur. Pressure on the bladder

causes pain; constipation is reported as general, and defecation causes emission of a few drops of blood from the urethra. In some cases there may be involvement of the prostate or of the vesiculæ seminales, causing spermatorrhœa, and in the latter event ova are found in the seminal discharge.

Urinary *fistula* is a frequent complication. This may form at any point near the genitalia but especially in the perineum near the scrotum; or on the posterior surface of the scrotum, where the fistulæ are usually multiple, and when the openings are numerous (up to 50 are recorded) some of these may be on the penis, over the pubes, near the anus, on the legs, etc. According to Milton, all simple fistulæ spring from the urethra; most fistulæ take origin from the pubic side or roof of the urethra, a few from the perineal side or floor; most floor fistulæ are formed just in front of the bulb, but some may be found in the penile urethra. Urethral

FIG. 61

Bilharziosis of the bladder. *Ur*, urethra; *Pl*, flat, hard, encrusted elevations; note the cauliflower-like growth in the bladder. (Looss.)

stricture is also encountered, especially (Milton) in case of floor fistulæ; the latter form from periurethral abscesses. The urethra may become solid so that the catheter cannot be passed.

As a result of the severer infections, the patient becomes anemic, debilitated and wasted, and may succumb to some intercurrent disease. Appendicitis, with blood-fluke eggs in the appendix, has been recorded in connection with vesical bilharziosis originating in Africa.

When bilharziosis occurs in women in Africa it is usually as a hematuria. In *vaginal* bilharziosis there is subacute vaginitis, the mucosa thickens (especially on the posterior surface of the vagina) and becomes hard and dry with longitudinal and transverse folds. Polypoid growths may be encountered, sometimes filling the entire vagina. The lesions may occur in the vagina without appearing in the bladder; bilharzia papilloma may be confused with epithelioma; a severe metritis may develop.

In *rectal bilharziosis* due to *S. mansoni*, fever develops early, with abdominal pains and a marked tenderness of the liver and spleen; later there may be urticaria, bronchitis, diarrhœa, and an eosinophilia of 36 to 76 per cent. After about one to three months, dysentery with 10 to 30 stools per day, or hemorrhages, or constipation may develop. There may also be hepatic and pancreatic cirrhosis, and hypertrophy of the spleen, also icterus and ascites; some patients become very irritable or forgetful, and the intelligence may decrease; weakness, vertigo, fever, purpura, and rectal fistulæ may appear; the mucous membrane becomes hypertrophied, excessively vascular, and of rich, red-velvet appearance; small or larger, simple or branching, soft, pile-like or coral-like growths are found from the sphincter up to the sigmoid flexure. There is excessive secretion of mucus and the patient feels as if his rectum were full and as if he wished to defecate. Little is passed, mixed with bloody mucus containing fluke-eggs. Repeated straining at stool causes prolapse of the rectum; at first this returns of itself but as time advances it must be helped back; finally the sphincter weakens and the rectum remains prolapsed; it becomes septic and may cause death.

FIG. 62

Bilharziosis of the rectum. *H*, cavities filled with blood. (Looss.)

In *Asiatic* bilharziosis, due to *S. japonicum*, there is a febrile period of about three to six weeks, with œdema, urticaria, epigastric pains, diarrhœa or constipation, and a marked eosinophilia (14 to 60 per cent.).

"Wading fever," in China, with "giant urticaria" and "slight bloody movements," has been explained as due to *S. japonicum*. When infection is contracted in youth, it may result in inhibiting physical development, as in hookworm disease. In the traumatic stage, with hepatic and splenic hypertrophy, the patient exhibits anemia, loss of weight, some fever, dysentery or constipation, ascites, œdema; eventually after three to four years, cachectic patients die. In the *cerebral* form, there may be difficulties in speech, headaches, mental troubles, trembling, vertigo, Jacksonian epilepsy, and hemiplegia.

Prognosis.—In case of light infection, the patient may not be inconvenienced. In simple uncomplicated cases, prognosis is not unfavorable but the possibility of new infection (since a careless patient is always a danger to himself as a source of infection) and the liability to septic infection, make bilharziosis a serious disease (Looss).

Diagnosis.—Definite diagnosis is based upon finding the characteristic eggs in the urine, feces, or tissues; presumptive diagnosis upon the gross lesions; tentative diagnosis (in endemic areas) upon symptoms; eosinophilia, in connection with symptoms, is suggestive but may be misleading (compare hookworms, trichiniasis, etc.). In the vesical type, the eggs are found especially in the last few drops forced out at the end of micturition; or in the last drops of urine in the catheter. In old cases, however, the eggs may not be present in the urine; if necessary, the surface of the bladder may be scratched and the shreds examined for eggs or the polypoid growths in the rectum may be removed and examined (Manson).

To distinguish concurrent affections note: Chyluria (chyle in the urine, a large clot with oil granules and globules, and *Filaria* will be found in the blood); calculus (do not mistake the hard, sandy, raised portions of the bladder wall for stones); gonorrhœa (history); and enlarged prostate. Floor-fistulæ may be mistaken for stones in the urethra, but the sound passes through and, as it is withdrawn, pus follows. In the rectum, distinguish bilharziosis from piles; large bilharzian tumors may resemble epithelioma or sarcoma.

Blood.—Le Dantec (1904) gives the leukocyte count as: Polymorphonuclears, 57 per cent.; mononuclears, 35 per cent.; eosinophiles, 8 per cent.

Death is due to exhaustion from pain and want of rest, together with debility consequent on the hemorrhage, aided by poisoning from absorption of septic matter or to pyonephrosis, pyemia, or uremia.

Treatment.—Some earlier authors have claimed that anthelminthic treatment is undesirable. Good results have been claimed by some authors from daily doses of male fern, santonin, quinine, or methylene blue. More recently, intravenous injections of tartar emetic have come into use and, although this is not without inconveniences, it is at present the method of choice, with emetine as alternative. An extensive literature exists on the antimony tartrate treatment in which Christopherson[1] has played a prominent role.

Antimony tartrate is administered in bilharziosis by two radically different techniques: (*a*) Intravenous injections, and (*b*) enemata. Both potassium antimony tartrate and sodium antimony tartrate are used; the latter is less toxic, more soluble, and quite as efficient as the former. It is contraindicated in too far advanced cases, in a feeble constitution, and in serious cardiac and renal diseases; some patients show a marked idiosyncrasy and cannot tolerate antimony. Its administration may cause a metallic taste, dryness of the mouth, a feeling of constriction in the throat, tightness of the chest, and later colicky pains; if these are severe, the succeeding dose should be reduced or at least not increased; giddiness, headache, sickness, and diarrhœa call for judgment in graduating the next dose; "rheumatic" pains, temporary though some-

[1] For one of his most recent summaries, see *The Lancet*, London, 1924, i, 1071.

times distressing, are very constant on the night following the fourth or fifth injection, and if severe may require a smaller succeeding dose.

(*a*) *Intravenous Injections.*—The technique varies in details, but authors agree in emphasizing the necessity of *slow* injections. If the drug is injected into the tissues, instead of into the lumen of the vein, a severe cellulitis may develop. Under ordinary circumstances, if the patient continues recumbent for half an hour after the injection he is able to walk home, but he should rest for the day; light food may be taken two hours after the treatment. (*a*) Dissolve one 10 gr.-tablet in 40 cc. of distilled water; add sodium chloride to make a physiological solution; 2 cc. contains the initial dose of $\frac{1}{2}$ gr., and 10 cc. the maximum single dose of $2\frac{1}{2}$ gr. The first dose for an adult is $\frac{1}{2}$ gr. (for children under ten years, $\frac{1}{4}$ gr.); increase the adult dose by $\frac{1}{2}$ gr. at each injection until the maximum dose of 2 or $2\frac{1}{2}$ gr. is reached, then repeat the maximum, unless contraindicated, at each succeeding injection. Give the intravenous injections two and a half hours after a light meal, when the stomach is neither distended by food nor the patient exhausted by hunger; treat on alternate days or three times a week. On the ninth day, the eggs in the urine appear granular; after a total of 20 gr. the urine is practically normal; a total of 25 to 30 gr. is usually necessary (in the adult) to kill the worms and the ova; if a cure is not effected by a total of 30 gr., suspend treatment and after an interval of rest give a second course. (*b*) Prepare a 1 per cent. solution in physiological saline, sterilize in the autoclave or through Chamberland filter; administer on alternate days. The (initial) dose is 5 centigrams and increases to 7.5, then to 10 centigrams; a total (cumulative) dose of 75 centigrams is tolerated. (*c*) Prepare a 2 per cent. solution in physiological saline; sterilize at 120° C. Administer for the first seven days, successively, 1.3 cc., 1.5 cc., 3 cc., 3 cc., 4.5 cc., 4.5 cc., 6 cc.; then 6 cc. on alternate days until the nineteenth day; the total dose is 1.2 gm. (*d*) Initial dose, 1 gr.; increase by $\frac{1}{2}$ gr. at each succeeding injection up to $2\frac{1}{2}$ gr. at the fourth injection; consecutive injections for the first six days, then alternate days. Aim to secure the cumulative effect of about 20 gr. of tartar emetic. In 1000 cases there were 10 deaths, but these were patients in very poor physical condition; of 630 cases, 20.6 per cent. received less than six doses; of 500 cases, 70 per cent. were cured.

(*b*) *Rectal Injections.*—Wilson (1922) argues that in rectal injections the drug is absorbed and enters the superior hemorrhoidal vein; part passes to the bladder wall and part by the portal vein to the liver. In this way it exerts its maximum action upon the parasites before entering the rest of the general circulation. He has administered up to a total of 104 gr. in 14 high enemata (first dose, 1 gr. in 100 cc. of water at body temperature; two days later, 2 gr.; then every other day for three weeks the dose increasing in series of 2, 3, 4, 5, etc. grains; the 12 gr.-dose is repeated twice, then two days later, 14 gr. The total amount of fluid is made up to about 1 or 2 oz. It is maintained that this technique is not inferior to the intravenous method, that it economizes time, is free from all risk, and that nausea and vomiting are less frequent. Cures are claimed after 4 to 14 enemata. Christopherson considers this method of administration as of doubtful value.

Emetine.—Christopherson considers emetine second to tartar emetic, while some authors prefer the emetine. Prolonged use of emetine is reported as causing fatty degeneration of the liver, kidneys, heart, and diaphragm, and as contraindicated in pregnancy. Tsykalas reports 90 per cent. cures in 2000 cases; he administered a total of 1 to 1.2 gm. in eight to ten days (0.1 to 0.12 gm. per day) and prefers these larger to smaller doses extending over a longer time.

Symptomatic or palliative treatment (rest, abundance of water, lavage) is instituted for local conditions; recourse to surgical treatment is had for the obstructive growths, etc.; cauterization is reported as giving good results.

Milton warns against lithotomy if not absolutely necessary, but he has good results from lithotrity. Perineal fistulæ are treated on general surgical principles. Hyperplasia in the vagina and cervix is treated by excision of thickened and infiltrated mucous membrane.

In rectal bilharziosis the irritation is allayed by local sedatives and astringent applications. The rectal tumors are removed as far as possible. In case of high tumors Milton destroys them by swabbing for about a minute with chloride of zinc solution 1 to 10, then drying out the excess with cotton followed by washing with copious salt solution.

Operation on the prolapsed rectum, avoiding the sphincter, is more or less successful in fresh cases, but not in advanced cases. It is often difficult to decide whether excision of the prolapsed portion is justifiable.

Prevention.—For *personal* prophylaxis in endemic areas; (1) avoid wading or bathing in waters suspected or known to be subject to contamination with excreta—theoretically easy, but practically often difficult; (2) bathe in water which has been stored for two days—also an easier measure theoretically than practically; (3) drink no water unless boiled or filtered. For *public* prophylaxis: (4) sewage treatment; (5) filtration plants and storage reservoirs; (6) destruction of snails (copper sulphate 1 to 5,000,000 destroys *Bulinus contortus* and *Planorbis boissyi;* 1 to 2,000,000 destroys *Lymnaea truncatula.* Ducks, geese, frogs, and carp feed on snails. Drainage.) Brumpt suggests the use of animals (cattle) as bait to attract and catch the cercariæ of *S. haematobium* and *S. mansoni.* Public health measures against *S. japonicum* are complicated by the fact that the snail involved is able to survive some (five or more) weeks out of water and after this period discharge live cercariæ.

OPHTHALMIC DISTOMATOSIS

Ophthalmic distomatosis has been reported for man on only two occasions: *Monostomulum lentis* (Gescheidt, 1833) is a trematode of uncertain systematic position which has been reported once, in Odessa, in the crystalline lens. Possibly it is an erratic liver-fluke. *Agamodistomum ophthalmobium* (Diesing, 1850) is also of doubtful systematic position (possibly an erratic liver-fluke). It is reported once, in Dresden, between the crystalline lens and its capsule.

TÆNIASIS—CESTODE INFECTION

Terminology.—*Taenia* was the original cestode genus (1758) and has served as the great collective genus of the tapeworms. It is now confined to cestodes of the type of *Taenia solium*, but the term teniasis is retained to denote any cestode infection. We may have two kinds of tæniasis: namely, (*a*) intestinal infection with the tapeworm stage, or (*b*) somatic infection with the larval stage. In some animals adult tapeworms are found in the gall ducts.

INTESTINAL TÆNIASIS—TAPEWORM[1] INFECTION

The day is past when a simple diagnosis of "tapeworm" is sufficient, for it may be a matter of importance, both to the physician and the patient, to establish what particular kind of tapeworm is present. Upon such determination may rest the question of the time of treatment, the precautions to be taken, and even—in exceptional cases—the risks to be run and the chances for complete recovery.

So far as is established, man seems to be the normal and sole host for the sexual stage of at least two of the large tapeworms, *Taenia saginata* and *T. solium*. Man, together with the dog, probably forms the normal host for a third large tapeworm, *Diphyllobothrium latum*. Man seems to be a normal host for the dwarf tapeworm (*Hymenolepis nana*); *H. fraterna* of rats seems to be distinguished from the form in man only as a physiological variety.

Occasionally, though rarely, as accidental host, man harbors the double-pored tapeworm (*Dipylidium caninum*) of dogs and cats, the flavo-punctate tapeworm (*Hymenolepis diminuta*) of rats, and the lanceolate tapeworm (*Drepanidotaenia lanceolata*) of ducks and geese. Various other tapeworms reported for man are: *Taenia confusa* (rare, in the United States), *T. philippina* (in Manila), *T. bremneri* (in Nigeria), *T. hominis* (in Aschabad), *T. africana* (East Africa), *Davainea madagascariensis* (occasionally in the tropics), *D. asiatica* (in Asiatic Russia), *Bertiella satyri*, *Diphyllobothrium cordatum* (in Greenland), *Diph. parvum* (in Tasmania or Syria), *Diplogonoporus grandis* (in Japan), *Dip. brauni* (in Rumania), *Braunia jassyensis* (in Jassy), etc.; too little at present is known of the occurrence of these species to permit a definite judgment as to whether man is their normal or simply an accidental host, except perhaps in the case of *Diph. cordatum* and *Bertiella satyri*, for which man seems to be an accidental host. Interesting as these infections are, it may be said that from a clinical point of view our knowledge of the adult tapeworms in man is based chiefly upon three large species (*Diph. latum*, *Taenia solium*, *T. saginata*) and one small species (*H. nana*). Of these the average practitioner in Australia, England and North America will come in contact especially with the fat tapeworm (*T. saginata*); he will

[1] For keys to and specific diagnoses and full synonymy of the various tapeworms of man see Stiles, 1906 *a*, pp. 1 to 104, Figs. 1 to 160. *Bulletin* 25, *Hygienic Laboratory, U. S. Public Health Service, Washington.* For more recent keys to genera, see Stiles and Hassall, 1926 a, *Bulletin* 142, *Hygienic Laboratory.* For detailed index to subject, see *Bulletin* 85, *Hygienic Laboratory*, etc.

doubtless meet infections with the dwarf tapeworm (*H. nana*), but will usually fail to recognize them, although in some parts of the United States he will probably have 5 or more cases of this parasite to 1 of the fat tapeworm; it is the exception that the pork-measle or armed tapeworm (*T. solium*) is found, while probably not one physician in a hundred in Australia, England, and North America has seen an infection with the broad tapeworm (*D. latum*), and if he does see such, it may be chiefly imported cases among Russians, Swedes, Finns, Germans, or in persons who have visited the more infected European or Asiatic localities; the broad tapeworm seems now, however, to have become endemic in the northern lake region of the United States.

All four of these more common species present certain points which should be borne in mind. The pork-measle tapeworm, though not common, is the most dangerous. The dwarf tapeworm is the most common in some localities, though its frequency in others is not established; although it is very small it may occur in large numbers and produce severe symptoms. The fat tapeworm is the most common of the larger forms; it may produce severe symptoms, is sometimes difficult to expel, but is not dangerous as compared with *T. solium*. The broad tapeworm may be associated with a more or less severe anemia.

The Fat Tapeworm.—*Taenia* (*Taeniarhynchus*) *saginata* Goeze, 1782.—**Geographical Distribution.**—Practically cosmopolitan.

Zoölogical Distribution.—The adult is known only for man. The larva (*Cysticercus bovis*) is found in cattle; it is also reported by several authors for man but doubts arise regarding the determinations except in 1 case reported by Fontan, 1919; experiments to grow it in apes, dogs, goats, hogs, rabbits, and sheep have been negative, but it is reported that Heller succeeded in infecting a sheep, and that Zenker and Heller infected young goats.

The Parasite.—The fat or unarmed tapeworm, *Taenia* (*Taeniarhynchus*)[1] *saginata*,[2] is one of the largest known cestodes, attaining a length of about 4 to 8 or 12 meters; the head is without hooks; there may be nearly two thousand segments present; only two ovaries are found in each mature segment; the uterus in the gravid segments has 15 to 35 slender dichotomous lateral branches each side of, and shorter than, the median stem; genital pores lateral (marginal), somewhat irregularly alternate; terminal segments attain 16 to 25 mm. long by 4 to 7 mm. broad; eggs with thick, dark, radially striated embryophore ("inner shell," or "shell" in most medical works), 30 to 40 by 20 to 30 μ. The segments usually escape singly and actively, forcing their way out of the anus.

[1] In zoölogical writings, a capitalized name inserted in parentheses between the generic and the specific names denotes subgenus. The present genus, *Taenia*, for instance, may be divided into the subgenera: *Taenia*, type *T. solium; Hydatigera seu Reditaenia*, type *T. taeniaeformis;* and *Taeniarhynchus*, type *T. saginata*. Subgenera are used in zoölogy for several purposes. Their chief use is to enable the classification of species into groups to which generic rank is not given; another use of subgenera is to foreshadow probable changes in the classification. When a genus is divided into subgenera, it is not necessary to cite the subgeneric name when referring to the species. Thus, *Taenia saginata* is as valid a citation as *Taenia* (*Taeniarhynchus*) *saginata*.

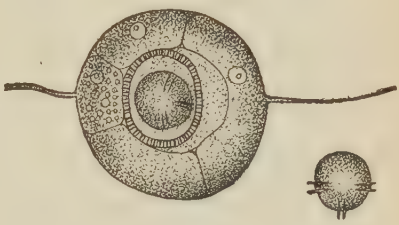
[2] Synonyms.—*Taenia solium* Linnaeus, 1758 (pro parte); *T. mediocanellata hominis*, seu *T. mediocanellata* seu *T. zittaviensis* Küchenmeister, 1852; *T. inermis* Moquin-Tandon, 1860.

Source of Infection.—This parasite is obtained through eating beef, especially the tongue and the muscles of mastication, infected with *Cysticercus bovis*.[1] Cattle become infected by swallowing the embryo (onchosphere), encased in its embryophore, in their food or in water contaminated directly or indirectly with infected human feces. Ransom has traced an unusually interesting instance of the infection of a number of cattle because of the poor drainage from soil-polluted ground.

FIG. 63

Gravid segment of beef-measle tapeworm (*Taenia saginata*), showing lateral branches of the uterus, enlarged. (Stiles.)

FIG. 64



Egg of beef-measle tapeworm (*Taenia saginata*) with thick egg shell (embryophore), containing the six-hooked embryo (onchosphere), enlarged. (Leuckart.)

Frequency.—This is the most common of the large tapeworms of man in North American and Europe (except in certain regions where *Diphyllobothrium latum* abounds), but it will doubtless gradually decrease in frequency because of the meat inspection and cold storage of beef. It is reported as exceedingly common in certain localities of Africa and Asia. It is more common in females than in males, and while it may be present in patients of almost any age, it is more common in people between twenty and forty. It is occasionally found in very young children who, by prescription, have been given raw beef. Usually only one specimen is present in a patient, but infections with from 1 to 59 worms are reported.

Duration.—Beyond the fact that persons may harbor this worm for a number of years, the longevity of this species is not established; considering the method by which the segments are formed, the age of the worm seems to be, theoretically, potentially almost indefinite.

Special Medical Features.—The fat tapeworm is not only more common than *T. solium*, but the consensus of opinion seems to be that it is more difficult to expel, despite the absence of hooks from the head. While clinical reports seem to show that anemia is more likely to result from *T. saginata* than from *T. solium*, and less likely than from *D. latum*, the fat tapeworm is really of much less importance than *T. solium*, for it does not

[1] SYNONYMS.—*Cysticercus taeniae-saginatae; C. bovis; C. taeniae-mediocanellatae; C. inermis* of various Germans and others.

combine with it the danger of cysticercosis which we may find associated with infection with *T. solium*. Hence, if treatment for *T. saginata* is not convenient at the time of diagnosis (as in case of pregnancy) this can be postponed without any special danger.

FIG. 65

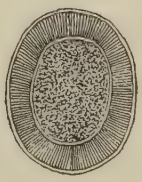
Gravid segment of *T. confusa*, to show the uterus. × 6. (Guyer.)

Differential Diagnosis.—In general it is unwise to attempt to distinguish *T. saginata* from *T. solium* on the microscopic examination of the eggs found in the feces. The author has examined the adult worms which various persons have positively determined by this method as being *T. solium* and in every case thus far the parasite has proved to be *T. saginata*. It is also unwise to rely only upon the form of the segments. A safer plan is to press the discharged segments between two pieces of glass, hold the preparation to the light, and count the lateral branches of the uterus. If the head is found, determine the presence (*T. solium*) or absence (*T. saginata*) of hooks.

Prevention.—Proper disposal of human feces should prevent the infection of cattle. A proper system of meat inspection[1] prevents the infection of man. Under the Federal meat inspection over 40,000 beef carcasses are retained annually on account of *Cysticercus bovis;* excessive infestations are condemned, but in slight and moderate infections the parasites are killed by refrigeration or pickle for twenty-one days, or by cold storage at 15° F. or below for six days, and the meat can be safely eaten. Thorough cooking also kills the cysticerci.

Taenia (Taeniarhynchus) abietina Wienland, 1858, has been reported only once—

FIG. 66



Onchosphere of same surrounded by embryophore, from uterus. × 660. (Guyer.)

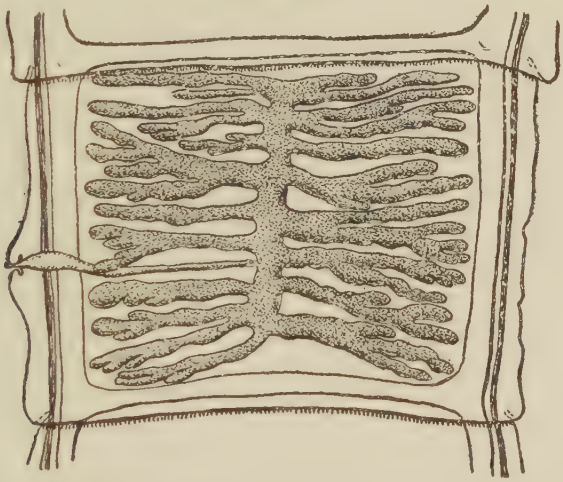
[1] See Stiles, 1898 *a*, pp. 77 to 83. *Bulletin* 19, *U. S. Bureau of Animal Industry.*

from an Indian, Lake Superior. Source of infection and even systematic status are not established. The head is unknown, but from the form of the uterus, some authors assume that this worm is either identical with or a variety of *T. saginata.*

Taenia (Taeniarhynchus) confusa Ward, 1896, has been found in Texas and Nebraska. It attains 5 to 8 meters in length; head unarmed; segments may attain 27 to 35 mm. long by 3.5 to 5 mm. broad, greatest breadth 8 to 10 mm.; ovaries 2, distinctly reniform; uterus with 14 to 18 short, thick, dichotomous lateral branches each side of median stem; eggs 39 to 30 μ. Thus far little is known regarding the history and clinical significance of this American tapeworm, which should be looked for especially in the Northwest.

Taenia (Taeniarhynchus) philippina Garrison, 1907, known only from the Philippines, attains 80 to 100 cm. in length, 1 cm. in breadth, and develops about 800 segments; ovaries 2, unequal; uterus with "numerous" dichotomous lateral pouches; embryophore 35 to 41 by 26 to 36 μ. Vector unknown.

FIG. 67



Gravid segment of pork-measle tapeworm (*T. solium*), showing the lateral branches of the uterus, enlarged. (Stiles.)

Taenia (Taeniarhynchus) africana Linstow, 1900, is a species closely allied to *T. saginata;* it occurs in the negro in German East Africa. The parasite attains 1.4 meters in length; scolex unarmed; segments about 600 in number, always broader than long, attaining 7 mm. in length by 12 to 15 mm. in breadth; uterus with 15 to 24 simple (not dichotomous) branches each side of, and longer than, the median stem; embryophore 31 to 39 by 33.8 μ. The life-cycle and source of infection are unknown but the zebu has fallen under suspicion as possibly representing the intermediate host.

Taenia (Taeniarhynchus) hominis Linstow, 1902, was found once, in Aschabad. The parasite measured 70 mm. long by 1.11 to 1.97 mm. broad. The scolex possesses a rudimentary rostellum without hooks;

suckers directed postero-anteriorly; caudad of suckers a circular ridge is present. The genital organs were not developed, but von Linstow considers that the indications are that this worm may attain as great length as *T. saginata*.

The Pork-measle Tapeworm.—*Taenia (Taenia) solium.*—**Geographical Distribution.**—Practically cosmopolitan, following the hog.

Zoölogical Distribution.—Adult known only for man; experiments to grow it in a monkey (*Macacus cynomolgus*) and in dogs, guinea-pigs, and rabbits have been negative. The larva (*Cysticercus cellulosae*[1]) is found especially in hogs; it is said that it may, occasionally, occur in sheep, but Ransom's investigations raise a question as to the correctness of the zoölogical determination; it is also said that it will develop in young dogs; it develops in man and is reported for various monkeys, the boar, roe deer, and the rat.

The Parasite.—The armed or pork-measle tapeworm, *Taenia (Taenia) solium*[2] (Linnaeus, 1758), is slightly smaller than the fat tapeworm; it does not usually measure over 2 to 3.5, 6 or 8 meters in length; the head is armed with a rostellum, bearing a double row of hooks, of larger and smaller size, 22 to 32 in number; genital pores lateral (marginal), irregularly alternate; mature segments contain 3 ovaries, due to the fact that the ovary on the pore-side of the segment is divided; the segments may attain 10 to 12 mm. in length by 5 to 6 mm. in breadth; 700 to 1000 segments may be present; in gravid segments, the median uterine stem possesses 5 to 15 lateral dichotomous branches each side; "eggs" (embryophore) very similar to those of *T. saginata*, 31 to 36 μ in diameter. The segments usually escape passively several joined together, in the feces.

Source of Infection.—This parasite is obtained by eating undercooked, underpickled or undercured pork or wild boar meat. The hogs become infected by eating human feces containing either gravid segments or the egg with its enclosed embryo, or from food or drink contaminated with these eggs. To build a privy over the pig-pen, as is done in rural districts, means the formation of an endless chain in the biology of this worm.

Frequency.—As has been shown by Leidy, Osler, and the writer, this is not frequently found in the United States and Canada, despite statements to the contrary. Of 300 tapeworms from man examined by the author from 1891 to 1895, 297 were *T. saginata* and none *T. solium*. Of 28 tapeworms (1905) examined by him in two New England museums, 23 were *T. saginata* (several were labelled *T. solium*), 4 were *D. latum*, and 1 was too poor to determine. From 1891 to 1905 the only authentic specimen of *T. solium* sent to the writer came from Germany. Osler reported 76 cases of the cysticercus in hogs out of 1000 examined in Montreal; American cases of cysticercosis in hogs and man due to this species are known, so that there can be no doubt regarding its occurrence in this country and authentic cases of *T. solium* in man have been recognized in the United States. *T. solium* is said to be rather common in Panama. The relative infrequency of authentic cases of the pork tape-

[1] Synonyms.—*T. cellulosae* Gmelin, 1790; *C. cellulosae* (Gmelin) Rudolphi, 1808.

[2] Synonyms.—*T. solium* Linnaeus, 1758 (after elimination of *T. saginata* and *T. hydatigena*).

worm in America is due probably to (*a*) national culinary habits, (*b*) the curing methods, (*c*) the federal meat inspection, and (*d*) the passive passage of the segments which thus escape attention. In Europe, *T. solium* is decreasing in frequency because of the meat inspection. It is not found in persons who do not eat pork. It is especially likely to be found in people who eat raw or rare pork. It may be found in patients of almost any age, but appears to be more common in persons between twenty and forty years.

Duration.—The longevity of the individual adult parasite is not definitely established, but it can doubtless live for years (ten to fifteen or more).

Fig. 68

Section of a tongue heavily infested with measles, natural size. (Stiles.)

Special Medical Features.—While less likely, according to clinical reports, to cause anemia than is *T. saginata* or *D. latum*, the fact is constantly to be held in mind that *T. solium* is dangerous especially because of the possibility of its producing cysticercosis in man. On account of this danger, it is much more important to treat promptly the infection with *T. solium* than the infection with any other tapeworm. Further, not only is a patient with *T. solium* a constant danger to himself, but also to other members of his family, and especially to anyone occupying the same bed with him. A patient with *T. solium* should never sleep in bed with another person, not only between the time of diagnosis and treatment, but also until a definite cure is established. He should be warned to be unusually careful in his personal habits, relative to washing his hands and cleaning his finger nails.

Prevention.—Feces from infected patients should be so disposed of that they cannot infect hogs; hogs heavily infected (severe hog-measles, acute cestode tuberculosis) should be destroyed, but if the infection is very light no valid hygienic objection can be raised against eating the meat *in case it is thoroughly cooked;* cold-storage is not so promptly effective

against this parasite as it is against *Cysticercus bovis*, for *C. cellulosae* has been found alive twenty-nine days after its host was slaughtered.

Taenia (Taenia) pisiformis (Bloch, 1780) is a tapeworm which dogs contract by eating rabbits infected with *Cysticercus pisiformis*. Vital (1874) reports this tapeworm in man, but legitimate doubts may arise regarding the correctness of the zoölogical determination, especially in view of the fact that Galli-Valerio (1898) was unable to infect himself with this species experimentally by swallowing the larval stage.

Taenia (Hydatigera) taeniaformis (Bloch, 1780) is a tapeworm which cats contract from eating mice containing *Cysticercus fasciolaris*. Krabbe thinks its occasional presence in man is possible, because in Jutland hashed raw mice are occasionally eaten as a remedy for retention of urine. No authentic case of such infection seems to be reported.

Taenia (Hydatigera) infantis Bacigalupo, 1922, described from the intestine of a child in Argentine, bears a remarkable resemblance to *T. taeniaeformis* (s. *crassicollis*) of cats.

Taenia (subg.?) bremneri Stephens, 1908, is imperfectly known, but is possibly a synonym of *T. saginata;* uterus with 22 to 24 ramified, lateral branches; eggs 38 by 30 μ. Vector unknown.

The Dwarf Tapeworm.— *Hymenolepis nana.*—**Geographical Distribution.**—In North America this parasite has been found very widely distributed, especially in the Gulf-Atlantic States. It is also reported for South America, Europe, Asia, Africa, and is probably more or less cosmopolitan.

Zoölogical Distribution.—Several authors (Grassi, Lutz, Ransom, and others) consider *H. nana fraterna*[1] Stiles, 1906, of rats and mice identical[2] with *H. nana* of man, but other authors (Moniez, Braun, Looss, Joyeux) are inclined to doubt this identity. Grassi, Looss, and the writer were unable to transmit the parasite of man to rats, but Woodland (1924) has recently transmitted it to 7 mice out of 30 to which he fed the ova.

The Parasite.—*H. nana*[3] (Siebold, 1852) is the smallest tapeworm known for man. It measures 5 to 80 mm. long by 0.5 to 0.9 mm. in maximum breadth, and is composed of 100 to 200 small segments. The rostellum is armed; there are 3 testes to each segment, and the genital pores are unilateral. The eggs have 2 distinct membranous shells; outer shell 30 to 68 μ in diameter; inner shell 16 to 34 μ, presenting at each pole a more or less conspicuous mammillate projection provided with filamentous appendages. The adults are found especially in the upper two-thirds or three-fourths of the ileum.

Source of Infection.—*H. nana* of man has been shown to have a direct development, without a separate intermediate host. *H. nana fraterna* develops in rats without any intermediate host; the eggs escape in the

[1] *H. murina* (Dupardin, 1845).

[2] From the hygienic point of view this assumption must be accepted until the zoölogical points in question are definitely settled; applied zoölogy is of course dependent upon theoretical zoölogy, but in doubtful cases we must be more conservative in applied than in abstract science.

[3] Synonyms.—(?) *Taenia murina* Dujardin, 1845 (not *T. murina* Gmelin, 1790, = *Cysticercus fasciolaris* Rudolphi); *T. nana* Siebold, 1852 (not Van Beneden, 1858); "*Hymenolepsis*" *nana* of various authors (misprint).

feces, and when swallowed, the onchosphere (embryo) bores into the villi of the intestine, where it develops within a few days into a larva (cercocystis); the latter reaches the lumen of the intestine and develops into the adult strobila. If the form in rats is identical with *H. nana*, man probably receives at least part of his infection from food soiled by the excrements of rats and mice. The large number of specimens sometimes found in man indicates that auto-infection occurs.

Frequency.—This parasite[1] is unquestionably much more common than is generally supposed, and indications are not lacking that, in certain parts of the world at least, it is the most common tapeworm of man. The author found it in 4 cases (2.5 per cent.) of about 160 persons examined between Richmond, Va., and Florida; his assistants found it in 6 cases (4.8 per cent.) of 123 children in a Washington orphanage. It is rather common in children coming to the U. S. Marine Hospital in Wilmington, N. C., and examinations by the Southern State Boards of Health show that it is widely distributed in this area; some authors report as high as 32.6 per cent. (Texas) to 39 per cent. (Florida) among children. Calandruccio estimates that in Sicily 10 per cent. of the children are infected. It has been found in patients from under five to over fifty years of age, but is more common in children from five to ten years old, and in boys than in girls. Crowded conditions, as in dormitories of orphanages, seem to be favorable to the spread of the parasite, which is more common in poorer than in well-to-do families. From one or two to several thousand worms may be found in a patient.

Duration.—The length of life of the individual parasite is not definitely established, but infections have been reported as lasting from two months to two and a half years.

Special Medical Significance.—Although this is a small tapeworm it seems an error to assume that it is of no significance. Light infections do not appear, *per se*, to be of much symptomatic importance, but they may lead to heavy infections productive of pronounced symptoms. The local lesions produced seem to be slight, and Mingazzini suggests that the symptoms are due to a toxin eliminated by the worm.

Treatment.—Male fern has been reported as the only remedy which had been useful in expelling this worm, while cusso, kamala, santonin, thymol, and pomegranate were reported as having failed. The writer has had fairly good results with the thymol treatment, and more recently oil of chenopodium is recorded as satisfactory.

Prevention.—On the assumption that *H. nana* in man is specifically identical with the small tapeworm of rats and mice, an important point in prevention lies in protecting food from these rodents. If a person is found to be infected, he should occupy a separate bed until fully cured.

Hymenolepis diminuta[2] (Rudolphi, 1819), the flavo-punctate tapeworm of rats, occasionally occurs in man. It measures 10 to 60 cm.

[1] For detailed discussion of the species of *Hymenolepis* which occur in man, together with summary of cases, see Ransom, 1904 *d*, pp. 1 to 138, Figs. 1 to 130. *Bulletin* 18, *Hygienic Laboratory, U. S. Public Health Service.*

[2] Synonyms.—*Taenia diminuta* Rudolphi, 1819; *Hymenolepis flavopunctata* Weinland, 1858; "*Hymenolepsis*" *flavopunctata* of several authors (misprint).

long by 2.5 to 4 mm. in maximum breadth, and is composed of 800 to 1300 segments. The head is unarmed; 3 testicles are present in each segment, and the genital pores are unilateral. The eggs are round to oval; the outer membrane (56 to 80 μ) may be radially striated; the inner membrane measures 24 to 40 by 20 to 36 μ. The larval stage is reported for insects, such as meal moths, earwigs, beetles, *Tenebrio*, and fleas. Cases are reported for man, for the United States, South America, and Europe.

Fig. 69

Head and strobila of dwarf tapeworm. (*Hymenolepsis nana*), enlarged. (Leuckart.)

Drepanidotaenia lanceolata[1] (Bloch, 1782), the lanceolate tapeworm of ducks and geese, has been reported once (in Germany) for man. This worm passes its larval stage in small crustaceans belonging to the family *Cyclopidae*.

Davainea (seu Raillietina) madagascariensis (Davaine, 1870) is known only for man, and has been reported 10 or 12 times (Comoro Islands, Mauritius, Siam, Nossi-Be, British Guiana, Philippines), chiefly in children. It measures 25 to 30 cm. long and is composed of 500 to 600 segments which attain 2 mm. long by 1.4 mm. broad; head with large round suckers, rostellum with 90 hooks; genital pores unilateral; calcareous corpuscles present; about 50 testicles present; eggs with 2 clear shells, the outer possessing 2 mammillate projections; eggs collect in 300 or 400 egg-

Fig. 70

Egg of *Hymenolepsis nana* as seen in fresh feces, enlarged. (Ransom, from Stiles.)

balls. The intermediate host is unknown, but Blanchard has suggested that possibly the cockroach (*Blatta orientalis*) plays this role. *D. demerariensis* Daniels, 1895, is accepted as a synonym of this species.

Davainea (seu Raillietina) asiatica (Linstow, 1901) was found once in Aschabad, Asiatic Russia. The scolex is unknown, but the anatomy of the fragment indicates that the worm is a *Davainea;* it measures 298 mm. long by 0.16 to 1.78 mm. broad and possesses about 750 segments; calcareous corpuscles absent; genital pores unilateral; ventral canals very

[1] Synonyms.—*T. lanceolata* Bloch, 1872; *Hymenolepis (Dilepis) lanceolata.*

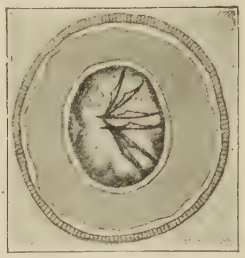
large; all genital organs are developed at 70 mm. from anterior end. The eggs collect in 68 to 70 egg-balls. Vector unknown.

Davainea (seu Raillietina) formosana Akashi, 1916, is reported from Formosa and Tokyo. It attains 25 cm. in length; terminal segments may attain 2.5 mm. in length; genital pores unilateral, near anterior corner of segment; eggs 99 by 46 μ. Vector unknown.

FIG. 71

Gravid segment of *H. diminuta*, enlarged. (Grassi.)

FIG. 72

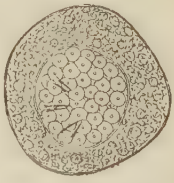


Egg of *H. diminuta* from man, greatly enlarged. (Bizzozero.)

Dipylidium caninum[1] (Linnaeus, 1758), the double-pored dog tapeworm, has been reported for man (chiefly children), about 75 times, at least 2 of the cases being recorded in American literature. It measures 15 to 40 cm. in length by 1.5 to 3 mm. in maximum breadth. The head is armed with hooks and there are 2 sets of genital organs to each segment. It is a very common parasite in dogs and the larval stage lives in dog lice (*Trichodectes canis*), the dog flea (*Ctenocephalus canis*) and the human flea (*Pulex irritans*). A very similar parasite occurs in cats.

Bertiella satyri (R. Blanchard, 1891), of the orangoutang has been reported once as having been expelled by a young girl. The inner shell of the egg has a rudimentary pyriform apparatus. Source of infection is unknown.

FIG. 73



Egg of *Dipylidium caninum*. Note the six hooks in the embryo, greatly enlarged. (Stiles.)

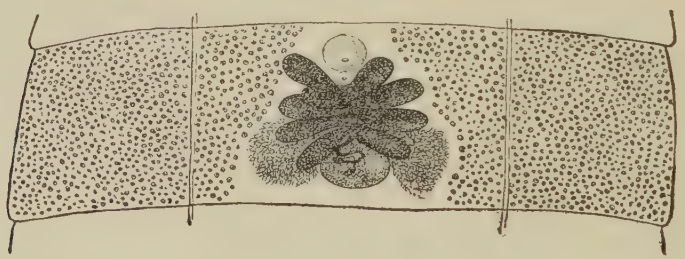
The Broad Tapeworm.—*Diphyllobothrium latum.*—**Geographical Distribution.**—This parasite is more common in the vicinity of large bodies of water (as in lake regions) than in regions of other topography. It is reported as especially common in Europe for the Russian Baltic provinces, Finland, Sweden, Denmark, Northeast Prussia, Switzerland, and Northern Italy, but it occurs also elsewhere, as in Belgium, Holland, Ireland, Northern France, etc. It is common in Japan and Turkestan, and is reported for Iceland, N'gami Lakes (Africa), Madagascar, South Africa, and the United States. It bids fair to become almost cosmopolitan, following the fresh-water fish diet, and the Lake region of North America will probably soon consider this as an established endemic parasite; in fact, it may be considered endemic there at present.

[1] SYNONYMS.—*Taenia canina; T. moniliformis* Pallas, 1781; *T. cucumerina* Bloch, 1782; *T. elliptica* Batsch, 1786.

Zoölogical Distribution.—The adult worm occurs in man, cats, dogs, and foxes (rare). The second larval stage (a "plerocercoid") attains a length of 30 mm. and is found in the muscles and various organs of twelve or more species of fresh-water fishes, particularly in the pike, ling, or burbot, perch, and several members of the salmon family; the first larval stage ("procercoid") develops in small fresh-water crustacea (*Cyclops strenuus*, *Diaptomus gracilis*) which become infected by the free swimming ciliated larva. Thus the cycle involve man (or other fish-eating mammal) to water to crustacean to fish to man (or other fish-eating mammal).

The Parasite.— *Diphyllobothrium latum*[1] (Linnaeus, 1758) attains 2 to 9 or 10 meters in length by 20 mm. in maximum breadth, it is usually grayish-yellow to brown in color, and composed of 3000 to 4200 segments, which are usually broader than long, especially in the anterior two-thirds of the strobila; posterior segments become quadrate or even longer than broad, and are especially characterized by the rosette spot (uterus) in the centre; three genital pores ventro-median; eggs 68 to 71 by 45 μ, with distinct operculum; laid during segmentation.

FIG. 74



Gravid segment of *D. latum*, showing the rosette uterus in the median line. × 6. (Leuckart.)

Source of Infection.—This tapeworm is contracted by eating raw or underdone fish.

Frequency.—Possibly about 100 cases of infection with this parasite have been recognized for the United States, not always among foreigners. In some parts of Europe it is reported as the most common tapeworm of man, the frequency varying from 0.8 to 10, 20, and, locally, even to more than 50 per cent. of the population. In Turkestan and Japan it is the most common tapeworm of man. Very probably it will become more commonly known in the United States, for now that special attention has been directed to it, it will be more frequently recognized, and further, it is certain that some of the fishes of our lake regions have become infected. It is observed more commonly in adults but may develop in persons of any age.

Duration.—The growth, after infection, is very rapid. According to Braun, the average daily increase for the first five weeks is 31 to 32 segments, involving 8 to 9 cm. increase in length; Zschokke found the

[1] SYNONYMS.—*Taenia lata* Linnaeus, 1758; *T. vulgaris* Linnaeus, 1758; *Bothriocephalus latus; Dibothrium latum; Bothriocephalus cristatus* Davaine, 1873; *Dibothriocephalus latus.*

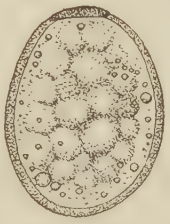
average daily increase in length to be 5.2 to 8.2 cm.; eggs may appear in feces twenty-four days after infection. Cases have been recorded of thirteen (Riley), fourteen (Mosler), and even twenty (Moneiz) years' duration.

Special Medical Significance.—There is a tendency to development of a severe anemia (Reyher, 1886, etc.) resembling pernicious anemia. Retinal hemorrhages have been reported in 50 per cent. of certain cases studied. This anemia is attributed by most authors to a toxin, supposed to be eliminated by the parasite, and a lethality as high as 16 per cent. was reported by one author. Schauman (1894) found the red corpuscles reduced to an average of 1,311,000 (in males) and 1,273,000 (in females) in 38 out of 72 cases; he also found fever (99° to 104° F.) in 81 per cent. of his cases; the pulse is often 90 or 120.

Fig. 75

Egg of *Diph. latum.* × 400. (Looss.)

Fig. 76



An egg of *Diph. grandis* taken from the uterus. × 440. (Ijima and Kurimoto.)

Clinical Diagnosis.—There should be little or no difficulty in diagnosing cases of this infection. As the uterus has a special uterine pore, eggs are constantly discharged from gravid segments and may be found in the feces. The segments show a tendency to be passed in small chains and ought not to be confused with those of the other tapeworms.

Prevention.—The feces of persons harboring this worm should not be allowed to gain access to fresh-water streams or lakes. Thorough cooking of fish will protect man from infection.

Ward (1906) has reported, but not described, a new bothriocephalid tapeworm as occurring in the United States.

Diphyllobothrium cordatum[1] (Leuckart, 1863) is reported in Greenland for man, dogs, bearded seal, and walrus. Its reported introduction into the vicinity of Dorpat and Berlin (Prussia) is based upon an error of zoölogical determination. It measures 80 to 115 cm. long with a maximum breadth of 7 to 8 mm. and is composed of about 600 segments; uterus with 6 to 8 lateral loops each side; the head is heart-shaped; neck absent; eggs 75 to 80 by 50 μ. It is probably contracted by eating fish.

Diphyllobothrium parvum (Stephens, 1908) appears to be rare. It is recorded for Tasmania, Persia, Roumania, Japan, and Minnesota. It is thicker and broader than *D. latum,* its operculated eggs are smaller

[1] Synonyms.—*Bothriocephalus cordatus* Leuckart, 1863; *Dibothriocephalus cordatus.*

(59 by 40 μ), and calcareous corpuscles are absent. Vector unknown, probably fish.

"Dibothriocephalus taenioides" (Leon, 1916), reported for man, in Roumania, is according to some authors an unusual specimen of *D. latum*. The segments are remarkably long and the uterus has only two or three slings.

Diplogonoporus grandis (Blanchard 1894) has been found in Japan. It may attain 10 meters in length, by 25 mm. in maximum breadth. It is similar to *Diphyllobothrium*, but has 2 complete sets of genital organs to each segment. The eggs are brownish, rather opaque, 63 by 48 to 50 μ. The source has not been demonstrated but infection probably takes place through eating fish.

Ashford, King and Gutierrez (1904, p. 92) report 1 case of this infection in Porto Rico but as the determination was made upon the eggs in the stools while the adult parasite was not seen, it may be well to reserve judgment regarding the zoölogical determination.

Symptoms.—Irregular appetite with occasional pains extending from the region of the stomach to the back; intestinal disturbance indicated by diarrhœa, colic, and constipation; anemia; poorly nourished condition, weakness, and inclination to faint.[1]

Diplogonoporus brauni (Leon, 1908) has been recorded in Rumania. It measures up to 29 cm. long, scolex 1 mm., bothria narrow, neck absent, segmentation indistinct, segments short and up to 6 mm. broad. Vector unknown, probably fish.

Ligula is a tapeworm which birds contract from eating fish. *L. cingulum* reported for man, is interpreted as possibly an erroneous determination of segments of a *Taenia*.

Braunia jassyensis (Leon, 1908) closely allied to *Ligula*, has been reported in Rumania. It measures up to 18 cm. long by 12 mm. broad, scolex triangular, bothria small, neck absent, external segmentation indistinct, a dorsal and a ventral median longitudinal groove present.

General Symptoms of Intestinal Tæniasis.—Reference has been made to the special medical significance of each form. In regard to the general clinical picture presented by patients harboring tapeworms, one noted clinician remarked that its chief characteristic is its lack of anything characteristic. That a person may harbor a tapeworm, especially one of the smaller species, and be unaware of the fact, cannot be doubted; and this has led some to minimize the importance of cestode infection. On the other hand, that tapeworm infection may result in severe symptoms is well established, for in numerous cases such symptoms have disappeared with the expulsion of the parasite; and this has led some observers to exaggerate its importance. We shall probably follow a justified mean between these extremes if we consider that the severity of the symptoms varies with the species of tapeworm present, with the number of the parasites, and with the age and general physical and nervous condition of the infected person. Some of the symptoms may be increased by salty or highly spiced food and decreased by milk or honey. The injury is

[1] For an account of this worm see Stiles and Taylor, 1902 *a*, pp. 43 to 47, Figs. 22 to 28. *Bulletin* 29, *U. S. Bureau Animal Industry*.

attributed to the following factors in particular: mechanical obstruction, injury or irritation to the intestinal mucosa, loss of food which goes to the parasite instead of to the host, and toxins produced by the worms or by the disintegration of segments.

The appetite varies; it may be decreased, increased to a point of insatiability or the two conditions may alternate; Hirsch reports loss of appetite in 6 per cent. of cases, bulimia in 10 per cent., capricious appetite in other cases.[1] Seeger records irregular appetite or bulimia in 31 per cent. (selected cases).

Salivation is often mentioned; Hirsch records it for 6 per cent. Eructation finds frequent mention; Hirsch reports it for 5 per cent. Nausea is common; Hirsch reports it in 13 per cent.; Seeger reports frequent nausea, with vomiting or feeling of faintness in 49 per cent. Vomiting may occur, and in some instances the tapeworm or portions of it have been vomited; this is particularly dangerous if the worm is *T. solium*.

Abdominal pains are very commonly complained of; they may be of the nature of colic or gastralgia; they are referred to different parts of the abdomen, are of varying severity, sometimes intermittent; there may be borborygmi, a sense of distortion or twisting in the bowels, or a sensation of a ball or weight rolling around in the abdomen following the movements of the body. Some patients present a pseudo-appendicitis which may recur more or less regularly; this is due in part at least to mechanical irritation as the segments lie in or pass by the appendix and disappears when the segments are passed per rectum. In experimental infection on myself the most pronounced and common symptom was that peculiar sensation one often has upon the sudden descent of an elevator; this occurred particularly while walking. Huber, in experiments upon himself, experienced a gnawing sensation in the epigastrium. Seeger reports abdominal pains of various sorts in 42 per cent., and peculiar sensations of movements in the abdomen in 16 per cent.; acute colic, 17 per cent.; Hirsch reports abdominal pains as common, colic in 14 per cent. Digestive troubles are reported by nearly all authors. Constipation (5 per cent., Hirsch), diarrhœa (6 per cent., Hirsch), or irregularity of bowels (3 per cent., Hirsch) may obtain. Seeger reports digestive troubles and irregularity of the bowels in 33 per cent.

Anemia is most likely to occur in infections with *Diphyllobothrium latum* less likely with *T. saginata*, and is said by some authors not to occur with *T. solium*.

Unequal pupils are commonly recorded; disorders in vision, as narrowing of visual field, amaurosis, monocular polyopia, are on record. Ringing or humming in the ears, disturbances in hearing, and deafness are mentioned. Headache is more or less common (14 per cent., Hirsch); Seeger

[1] The statistics quoted from Cobbold (1883 *a*), Hirsch (1879), and Seeger (1852) are based upon infections with large tapeworms and to a certain extent represent selected cases. Ransom (1904 *d*) published a very instructive compilation of the symptoms reported for 49 cases of infection with the dwarf tapeworm; the reader is referred to Ransom's paper for details since so many complex factors enter into consideration that to quote these details, not all from one observer, in comparison with the statistics quoted for the large tapeworms, would require a lengthy discussion. In general it may be said that the same symptoms recorded for the large tapeworms may occur with the dwarf tapeworm.

reports periodical and habitual headache, usually unilateral (19 per cent.) and vague pains in different parts of body (11 per cent.). Itching and dryness of the nose and epistaxis are more or less common. According to Davaine, anal pruritus, like nasal pruritus, may be attributed to a sympathetic influence, but is usually due to irritation of the lining of the lower part of the intestine produced by contact and movement of detached segments; nasal pruritus (12 per cent., Hirsch) is less frequent than anal pruritus (19 per cent., Hirsch), but it is rare that a patient has neither (Davaine).

Emaciation is common when the infection is of long standing and may be accompanied by bloating and distention of the abdomen. There may be gradual loss of strength, a general and continued weariness, or weakness, especially in the knees; cramps and pains in the limbs may be severe enough to interfere with the usual occupation (Davaine). Disturbed sleep is common; insomnia may be persistent. Vertigo, which many authors mention, Seeger records in 15 and Hirsch in 16 per cent. Epileptiform attacks (*epilepsia taeniosa*) are mentioned by a number of authors; the symptom is rare (1 per cent., Hirsch), and may occur in patients as young as three years (Comby); the attacks do not attain the severity of true epilepsy; the aura is of long duration, the convulsions may last ten to fifteen minutes and the stage of coma is equally long; all stages are more prolonged than in ordinary epilepsy (Comby) and there is a tendency to periodicity (Martha, 1892).

Treatment.—Emphasis may again be laid upon the point that if *T. solium* is present, especially in patients with a tendency to vomit, no time should be lost in expelling the worm; in case of infection with any of the other species mentioned, prompt treatment is advisable on general principles but a postponement for a few days or even a few weeks or months is of less serious moment. During such period, however, the patient should take care not to defecate in any place where the eggs in his discharge can gain access to the intermediate host.

Special precautions are to be taken, or the treatment is to be indefinitely postponed, in pregnancy, or in patients debilitated from other cause than tæniasis, and in convalescence, tuberculosis, and cancer.

In treatment, four points in particular are to be held in mind: (1) Make it clear to the patient *from the outset* that the expulsion of the worm is to some extent a matter of chance, and that while it is hoped that only one treatment will be necessary, no physician can possibly foresee whether or not it may be necessary to repeat medication several or many times, especially for *T. saginata*, before a cure is effected; (2) the clearer the bowels are the better the chances for expelling the parasites; (3) the older the drugs the less are the chances for success; (4) the tapeworm is an animal with a highly organized nervous system. Corresponding to these important facts, there are four periods in treatment.

1. **Mental Attitude of Patient.**—Gain the confidence of the patient, put his mind at rest, convince him that the disgrace in tapeworm infection does not consist in becoming infected but in not making an effort, by treatment or by care in defecation, to prevent spreading the parasite to other persons.

2. **Preparatory Treatment.**—Place the patient on a light diet for two or three days, avoiding bread and vegetables and such food as is likely to increase the fecal material; allow chiefly liquid diet, milk, broths, eggs, etc. Many physicians prefer to withhold food absolutely for twenty-four hours preceding the administration of the anthelmintic. At the same time give a mild laxative, such as a few doses of sulphate of soda, or a teaspoonful of compound licorice powder in the mornings, and take precaution to empty the bowels thoroughly, as by a saline purgative the night before the anthelmintic treatment, and enemata the night before and the morning of treatment. The object of this is twofold: the smaller amount of contents in the small intestines the less the tapeworm is protected from the drug; and if the worm meets with an obstruction as it descends, it may have a chance to recover its hold and thus remain in the intestines. Some authors advise a salad of dried herring, garlic, and onion the night before treatment.

3. **Anthelmintic Period.**—Early in the morning, following the period of preparation, coffee may be allowed but no solid food. Then take any one of the standard tæniafuges, provided it is fresh. For the comfort of the patient it is well for him to remain in bed or on a couch during this period, as various disagreeable symptoms (syncope, vertigo, vomiting) may otherwise arise.

Of the numerous tapeworm remedies, certain are recognized as more or less standard, but it would be difficult to obtain a great majority vote for any one of them to the exclusion of the others. The following are among those which are most popular:

Male Fern.—This is perhaps the most commonly used drug in this country and parts of Europe for the expulsion of *Taenia* and *Diphyllobothrium*. In Europe larger doses are administered than in America. Its oleoresin or ethereal extract is usually given and should be fresh. The dose is 2 to 8 gm. ($\frac{1}{2}$ to 2 drams) either in a simple syrup or in capsules, which may be coated with keratin to prevent their solution in the stomach and thus have the drug reach the worm in more concentrated form; the capsules are taken at intervals of about fifteen minutes. In an overdose, male fern is a distinct poison and it is reported that 24 gm. (6 drams) have caused death. Some authors advise that the dose should never exceed 10 gm. ($2\frac{1}{2}$ drams), while others maintain that doses higher than 8 gm. (2 drams) are unnecessary and not devoid of danger. Authors also advise against its administration either twice on the same day or two days in succession and on an absolutely empty stomach. Some authors advise its administration in pills. The last dose should be followed in thirty to sixty minutes by a full dose of salts (as magnesium sulphate) or calomel and salts, rather than with oil which increases its absorption.

Cusso (*Kosso or Kousso*).—This drug is used most frequently in certain parts of Africa and is highly recommended by several prominent authors. It must be quite fresh. It should never be given in case of pregnancy. Dose 20[1] gm. (5 drams) for *T. solium*, 30 gm. (7.5 drams) for *T. saginata*.

[1] Some authors advise only one-fourth to one-half this amount, but writers who are high in the praise of cusso give large doses.

There are several "best" methods of administering it. One is to make an infusion in 240 cc. (8 ounces) of water; a more pleasant method is to give 5 gm. (75 gr.) in a glass of white wine every half hour until four doses are taken; or it may be mixed with honey, enclosed in capsules, compressed into tablets, or combined with male fern.

Generally this requires no purgative but if no movement of the bowels has taken place after six hours, castor oil, compound jalap powder, or elaterium is given.

Kamala.—Kamala is administered in doses of 4 to 8 gm. (1 to 2 drams), in syrup of cinnamon water, sweetened coffee or tea, or the fluidextract (2 to 4 cc.—½ to 1 dram) is given. It is purgative and may cause nausea, vomiting, and griping.

Pomegranate Bark (Active Principle Pelletierine).—Hemmeter recommends that 50 gm. (1⅔ ounces) of the bark be macerated for twenty-four hours in 500 cc. (16 ounces) of water; the infusion evaporated down to 250 c.c. (8 ounces) and 30 gm. (1 ounce) of syrup of orange peel added; it is to be taken in two parts. It often causes nausea, giddiness or faintness. The fluidextract, 2 to 8 cc. (½ to 2 drams), is a more convenient preparation. Tanret has shown that the proportions of alkaloids in the bark vary according to several factors (climate, age of plant, season of collecting, etc.); he isolated two alkaloids (pelletierine and isopelletierine) which are about equally active against tapeworms, and two (methylpelletierine and pseudopelletierine) which are inactive.

Pelletierine tannate, which is very disagreeable to take, is recommended in doses varying from 0.12 to 1.5 gm. (2 to 23 gr.), but the tendency is to the lower doses, 0.12 to 0.52 gm. (2 to 8 gr.). *Pelletierine sulphate* alone is reported as effective in only about 35 per cent. of cases; it was formerly administered in doses of 0.5 to 0.7 gm. (7 to 10 gr.), but the adult maximum dose is now quite generally reduced to 0.3 gm. (5 gr.); it is less suited (more toxic) to children ten to twelve years of age, for whom the dose is reduced to 0.15 to 0.2 gm. (2.3 to 3 gr.).

On the premise that the sulphate is aborbed by the gastric mucosa, and therefore does not reach the parasite, Tanret advised that tannin be added to pelletierine sulphate but in smaller proportion than is found in pelletierine tannate, and it is this combination (sometimes, but erroneously, called "pelletierine tannate") which represents Tanret's pelletierine and which has gained such high repute because of its very high (nearly 100 per cent.) efficiency. The writer has used this repeatedly and always with success. One of the formulæ (for adult) reads: Pelletierine sulphate 0.25 gm. (3.8 gr.) + extract of catechu (for the tannin) 1 gm. (15 minims) [another formula gives 0.34 gm. (5 gr.) tannin] + distilled water 15 cc. (½ ounce) + syrup of bitter orange peel 25 cc. (6 drams). Follow in one half hour with 40 to 60 gm. (1¼ to 2 ounces) castor oil. This is very active and may cause dizziness, vomiting, headache and disturbances of vision. If the imported "Tanret" is used, it is well to insist upon stock of fresh importation. One routine is: (1) Clear bowels with enema or laxative; (2) very light evening meal (milk diet); (3) early next morning, pelletierine; remain recumbent as dizziness is more likely to develop if patient is up; (4) fifteen minutes after drug, a glass of water (transitory

dizziness is likely to develop about this time); (5) one half hour later, a brisk cathartic, as compound tincture of jalap; (6) pass worm into warm water; the worm is usually expelled within two to four hours after taking the pelletierine; if not passed promptly, administer enema. Some authors give ½ ounce of magnesium sulphate twenty minutes before and the same dose twenty minutes after the pelletierine.

Decorticated Pumpkin Seed.—This is an old remedy, which has been known to expel *T. saginata* when the foregoing drugs have failed; it is the safest and a good drug for children. It is given in various ways: (*a*) 30 to 120 gm. (1 to 4 ounces) of the seeds are crushed and given in a strained emulsion followed by a brisk purgative. (*b*) The seeds are made into an electuary. (*c*) Seeds are carried in the pocket and eaten at short intervals for two or three days, until the worm passes. Some authors advise that pumpkin seed be preceded by castor oil or by magnesium citrate, this to be repeated two hours after the anthelmintic if the tapeworm has not been expelled.

Santonin is advised by some authors, but the writer, in experiments upon himself (with *T. saginata*) found it useless. *Thymol* has been recommended, but in laboratory experiments upon dogs, the writer failed to obtain positive results (infection with *Dipylidium caninum*); this drug has, however, given fairly good results at the Marine Hospital in Wilmington, N. C., in infections with *Hymenolepis nana*. Naphthalin has its admirers (dose 0.1 to 0.6 gm.—1.5 to 9 gr.—followed in an hour by a cathartic). *Cocoanut* has been gaining in repute; the entire milk and meat of one cocoanut are taken, followed by a purge. Chloroform, oil of turpentine (with equal or twice the quantity of castor oil), zinc filings in syrup, oil of pine needles, and various other drugs have their advocates.

4. **Expulsion.**—The patient should use a vessel containing *warm* water while passing the worm and under no circumstances pass it into a water-closet, a privy, or a cold chamber. If the worm comes in contact with a cold object, while a portion of its body is still in the warm intestines, it may contract so suddenly and violently as to break; the head may thus remain in the bowels. The patient should be further instructed not to pull on the worm, should this be coming slowly, but to use injections of warm water. If the physician is present during the passage of the worm, the *parasite* is sometimes given an injection of morphine. Finally the patient should submit the entire stool for examination. Search is made for the head,[1] to determine whether the treatment has been successful. Should the head not be found, it is still possible that it has been passed, so that it is unnecessary to repeat treatment until (after several months) segments or eggs again appear in the stools.

Treatment of Children.—The treatment of children is attended with greater difficulty than the treatment of adults. Comby advises cusso, 10 gm. (2.5 drams), or decoction of fresh pomegranate bark, 15 to 20 gm. (4 to 5 drams), or ethereal extract of male fern, 4 to 6 gm. (1 to 1.5

[1] The entire stool containing the worm may be placed in a double layer of cheese-cloth; the margins are gathered together and fastened on a faucet; water is allowed to run slowly until the content of the cheese-cloth bag is fairly clean; then the residuum is placed in a bowl or an evaporating dish and examined for the head.

drams), or pumpkin seed in emulsion 50 to 60 gm. (1⅔ to 2 ounces). Comby gives ethereal extract of male fern, 4 gm. (1 dram), essence of turpentine, 1 gm. (15 minims), syrup of orange flower 30 gm. (1 ounce), peppermint water, 70 cc. (2.33 ounces); taken at one dose by child, aged five to ten years, and followed in one-half an hour by 15 to 20 gm. (3¾ to 5 drams) of castor oil (see, however, pp. 547, 574). French prefers, for children, drugs in the following order: pumpkin seed mush, cocoanut, belack oxid of copper, pelletierine.

SOMATIC TÆNIASIS

Somatic tæniasis, due to infection with the larval stage of tapeworms, may be of four kinds (in order of their importance): hydatid disease, due to infection with the larval *Echinococcus granulosus;* cysticercosis, due to infection with the larval *Taenia solium,* known as *Cysticercus cellulosae;* infection with bothriocephalid larvæ, classified as *Sparganum mansoni, S. baxteri,* and *S. proliferum;* and (rare) infection with *Multiceps* (syn. *Coenurus*).

Sparganum shows at most 2, elongate, suckers, or none at all; *Cysticercus* show s 1 head, with 4 cup-shaped suckers; *Multiceps* shows many heads, each with 4 suckers; *Echinococcus* shows many heads (in brood capsules), each with 4 suckers, and the cuticle of the cyst is thick (if the cyst is cut, it turns inside out, while in *Cysticercus* and *Multiceps* the cyst collapses).

Cysticercosis or Infection with Larval Taenia solium.—The Larval Parasite.—In the early days of heminthology, what we now know to be the larval stage of *Taenia solium* was supposed to represent a distinct species of animal, to which the name *Cysticercus cellulosae* was given. This larva is an elliptical, translucid, bladder-like structure, 6 to 12 mm. long by 5 to 10 mm. broad, with a white spot at its equator, due to the invaginated head. While it usually agrees with the same organism as found in hogs, it may (particularly when located in the subarachnoidal spaces) grow to a larger size and assume an irregularly branched form, described as *C. racemosus.* The parasite inhabits the subcutaneous connective tissue, muscles, brain (may last up to twenty-three years, average three to six years, generally fatal), spinal canal, eye (cases recorded with duration up to twenty years), heart, lymphatic glands, tongue, liver, bones, lungs, kidney, mammary gland, or prepuce, producing symptoms which vary with the location and number of parasites present. In 907 cases (Vosgien) 807 showed infection of only one organ and 100 of several organs; of the 807 single-organ infections, 372 (46 per cent.) were in the eye; 230 (41 per cent.) in the nervous system; 51 (6 per cent.) in the skin and connective tissue; 28 (3 per cent.) in the muscles, and 26 (3 per cent.) in other organs. In some cases, especially in very light infections, symptoms may not be observed and the infection is discovered at autopsy. In other instances, particularly in case of location in the brain or eye, the infection is of more importance and in case of cerebral or cardiac infection it may result fatally. If the parasite is in the eye, it is likely to be discovered by the ophthalmologist. In cerebral infection the symptoms vary according to the location; in case of continued pain in the head, visual

disorders, mental disorders, with depression and confusion or dizziness, unilateral paralysis, epileptiform, subacute, cumulative spasms, especially in patients over forty years of age, and showing concurrent adult *Taenia solium* in the intestine, or recent history of such intestinal infection, the possibility of infection with the larval stage is to be borne in mind. In 197 cases (Vosgien) symptoms were reported as follows: Headache (115), paralysis (62), epilepsy (52), convulsions (46), vomiting (42), vertigo (41), syncope (40), weakness in legs (30), agitation (26), intelligence affected (25), eyesight affected (25), general weakness (20), anorexia (20), cramps (20), negative (20), buzzing in ears (19), relaxing of sphincters (18), loss of memory (17), mental disturbances (17), somnolence (17) and trouble of speech (14).

It takes about three months for the parasite to develop from the six-hooked embryo (onchosphere) to the bladder-worm stage, which may live in man as long as twenty years. A patient may harbor from one to several thousand bladder worms, the heavy infections probably representing cases in which an entire segment of the tapeworm has gained access to the stomach through the pylorus. Cysticercosis is decreasing with the decrease of the adult worm; the latter is decreasing as a result of meat inspection and better curing and cooking of pork. Cysticercosis in man varies according to the frequency of the adult parasite, *T. solium*, in man; it appears to be relatively rare in the United States, but more common in countries like Northern and Eastern Germany, where raw pork is eaten.

There is no medical treatment; Feletti (1894 *a*) claims good results with male fern, 1 to 3 gm. (15 to 45 gr.) for several days, but his conclusions require confirmation. Surgical interference may be resorted to if the parasite can be located; cases of extractions of bladder worms from the eye are recorded.

Cysticercus bovis, the larval stage of *T. saginata*, is alleged to have occurred in man, but as *C. cellulosae* may lose its hooks and thus resemble the larval stage of *T. saginata*, doubts arise regarding the correctness of the determinations; Fontan's (1919) case of its presence in the mammary region of a man, who harbored an intestinal *T. saginata*, is accepted by Brumpt. *C. acanthotrias* Weinland, 1858, characterized by the presence of three rows of hooks on the head, and taken as the type of a special genus *Acanthotrias*, is now interpreted as simply an anomaly of *C. cellulosae*. *T. hydatigena* (Batsch, 1786) is a tapeworm very closely allied to *T. solium*, with which it was for years confused; the mature worm lives in dogs; the larval stage, known as *C. tenuicollis*, is found in cattle, sheep, hogs, etc., and is reported for certain monkeys; the cysticercus has also been reported for man, but the correctness of the zoölogical determination has been called into question. The reported presence, in man, of *Cyst. fasciolaris*, of mice and rats, the larval stage of *T. taeniaeformis* (s. *crassicollis*) of cats, is subject to confirmation. Likewise *sub judice* is the reported presence, in man, of *C. pisiformis*, a larval bladder worm of rabbits which develops into *T. pisiformis* (s. *serrata*) of dogs. *C. visceralis* Gmelin, 1790, (syn. *C. v. treutleri* 1819) has not been reported for man for more than a century and is today considered a doubtful species.

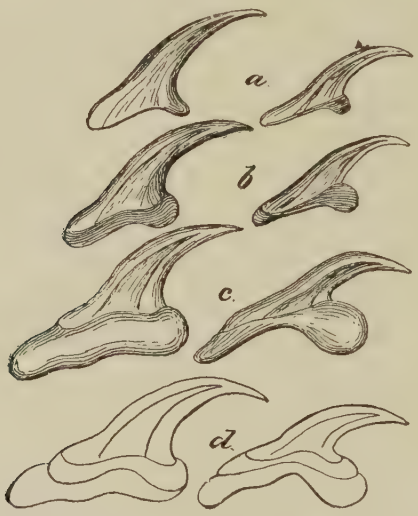
Multiceps differs from *Cysticercus* in having many heads (but not brood capsules) forming on the wall of the bladder worm. This genus causes "gid" ("turn sick") in sheep, but it is very rare in man.

Multiceps multiceps (Leske, 1780) (syn. *Coenurus cerebralis*), in the brain of sheep, is the larval stage of a tapeworm of canines. This larva has been recently reported in a fatal case in the brain of man in Europe, with pressure symptom of brain tumor.

Multiceps glomeratus (Railliet and Henry, 1915) of the gerbil, has been reported, in 1 case, in the intercostal muscles of man, in Nigeria, Africa.

Coenurus lowzowi (Lindemann, 1867) reported somewhat indefinitely for man, is interpreted as a synonym of *Multiceps serialis* which occurs in rabbits and is the larval stage of a tapeworm of canines.

FIG. 77



Hooks of hydatid tapeworm: *a*, from a hydatid; *b*, three weeks after feeding to a dog *c*, from an adult; *d*, combined figures of *a* to *c*, showing the gradual changes in form. × 600. (Leuckart.)

Echinococcosis: Echinococcus Disease; Hydatid Disease.—Geographical Distribution.—*Echinococcus* differs from both *Cysticercus* and *Multiceps* in the presence of a thick (instead of thin) external cuticle and in that the heads form in brood capsules instead of on the cyst wall. The adult tapeworm (in canines) has only 3 or 4 segments. This infection is practically cosmopolitan, but is reported especially in Iceland, certain parts of Germany, and in Australia. Many of the cases reported for the United States have occurred in immigrants who were doubtless infected before they came here, but we also have the parasite as part of our American fauna.

Zoölogical Distribution.—The adult tapeworm occurs in the upper half of the small intestine, but never close to the stomach, of dogs, wolves, jackals, *Canis dingo*, and it can develop in cats. The larval stage occurs in quite a number of domesticated animals, as sheep, cattle, hogs, and also

in certain wild animals, being reported from twenty-seven species of mammals. From the public health point of view it is especially the dog, sheep, cattle, and swine which come into consideration. Man is probably an accidental though not a rare host.

The Parasite.—It is at present an open question whether one, two, or three distinct species or varieties of echinococcus should be recognized. Most European zoölogists admit only one species, commonly known as *T. echinococcus* (Zeder, 1803) Siebold, 1853; American writers agree with Weinland that it is well to place this in a distinct genus; if this is done the correct name of the species is *Echinococcus granulosus*[1] (Batsch, 1786) Zeder, 1803. This is one of the smallest tapeworms known. It is composed of a head with 28 to 50 hooks, a short neck, and 3 or 4 segments; the first segment is immature, the second is mature, the last segment is gravid and it composes about ½ (2 mm.) of the total length (2.5 to 6 mm.) of the worm. The larval stage of this worm is the largest larval cestode known, and is the *Echinococcus*[2] or *Echinococcus* hydatid of medical and zoölogical authors. This may assume a number of different variations in growth. One of the peculiar extreme forms, the multilocular echinococcus, is recognized by some authors as a distinct parasite but many writers question its right to distinct rank. It seems to the writer that the present evidence, based largely upon geographical distribution and the larva, more than the adult stage, entitles it to rank as a sub-species, possibly as a species. If recognized as of sub-specific rank the correct name is *Echinococcus granulosus multilocularis*;[3] if recognized as a distinct species the correct name is *Echinococcus multilocularis* Leuckart, 1863. The finer points of distinction between the adult of this form and the typical form call for further investigation; the larval form or multilocular echinococcus is the "Gallertkrebs," "alveolar colloid" or "colloid cancer," usually found in the liver and reported in man, especially for Russia, Bavaria, Switzerland, Wurtemberg, Austria, the Alps, and Baden.

Von Ledenfeld (1886) states that an echinococcus tapeworm occurs in the dingo in Australia and may attain 10 to 30 mm. in length. The writer has not examined these worms, but unless confusion has here occurred with some other species, he would incline to the view that this parasite represents a distinct species.

Life Cycle of the Parasite and Source of Infection.—The gravid, terminal segment of the tapeworm is discharged in the feces of the dog, and the egg, which is said not to be very resistant, gains access to the intermediate host (sheep, cattle, hogs, man, etc.) through contaminated food or drinking water, or in the case of man, possibly also from hands soiled while petting dogs. Upon arriving in the stomach, the oncosphere (six-hooked embryo) escapes from the shell and, by means of its hooks,

[1] Generic Synonyms.—*Echinococcus* Rudolphi, 1802; *Acephalocystis* Laennec, 1804; *Echinococcifer* Weinland, 1856; *Liococcus* Brems., 1819; *Splanchnococcus* Brems., 1819; ? *Sphaeridion* Goodsir, 1844.

Specific Synonyms.—Adult: *Taenia nana* van Beneden, 1861 (not Siebold, 1853); *T. echinococcus; Echinococcifer echinococcus.*

[2] *E. polymorphus; E. unilocularis; E. cysticus.*

[3] Synonyms.—*Echinococcus alveolaris; E. multilocularis exulcerans; E. osteoklastes.*

bores its way through the wall of the stomach or of the small intestine, and may enter either the lymphatic channels or the veins; reaching the liver *via* the portal system, many of the parasites develop there; those which reach the right heart pass to the lungs and may develop there; as the embryos (20 to 25 μ in diameter) may stretch until they can pass

FIG. 78

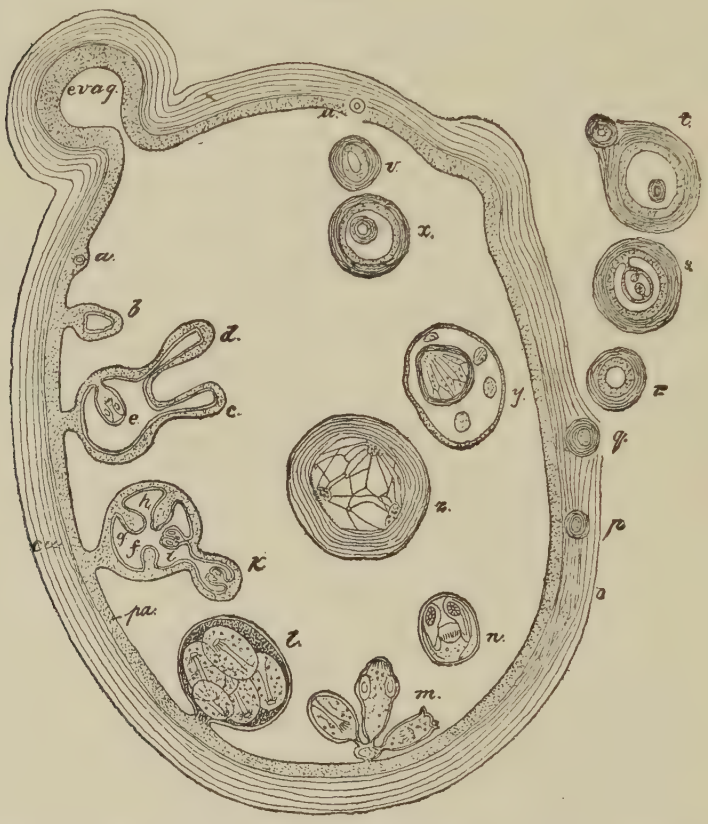


Diagram of an Echinococcus hydatid: *cu*, thick external cuticle; *pa*, parenchyma (germinal) layer; *c*, *d*, *e*, development of the heads according to Leuckart; *f*, *g*, *h*, *i*, *k*, development of the heads according to Moniez; *l*, fully developed brood capsule with heads; *m*, the brood capsule has ruptured, and the heads hang in the lumen of the hydatid; *n*, liberated head floating in the hydatid; *o*, *p*, *q*, *r*, *s*, mode of formation of secondary exogenous daughter-cyst; *t*, daughter-cyst, with one endogenous and one exogenous granddaughter-cyst; *u*, *v*, *x*, formation of endogenous cyst, after Kuhn and Davaine; *y*, *z*, formation of endogenous daughter-cysts, after Naunyn and Leuckart; *y*, at the expense of a head; *z*, from a brood capsule; *evag.*, constricted portion of the mother-cyst. (R. Blanchard, slightly modified.)

through almost any space which a red blood corpuscle can pass, some of them leave the lung and reach other organs of the body. The embryo comes to rest and increases very slowly in size; it presents a thick outer cuticle and an inner parenchymatic layer surrounding a cavity containing a toxic fluid which, if the cyst is ruptured, may cause (apparently by anaphylaxis) serious symptoms and even death. An outer connective-

tissue cyst is furnished by the host. This simple form is known as an *Acephalocystis*[1] Laennec, 1804. Brood capsules arise from the parenchymatic layers and hang into the cavity; heads form in these brood capsules. If this stage is fed to dogs each head develops into a mature tapeworm in four to ten weeks; heavy infections may cause a pseudorabies or an intense catarrhal inflammation of the intestine which may be fatal in a few days. The growth of the hydatid need not stop at the stage last mentioned but daughter-cysts and even granddaughter-cysts may form and fall into the cavity of the mother-cyst; this variation represents the endogenous echinococcus,[2] and is the more common variation as it occurs in man; it may attain 22 to 32 pounds in weight; the daughter-cysts may be numerous, "twenty-five to fifty" or up to "thousands." In still other cases the daughter-cysts pass outside of the mother-cyst into the surrounding tissue, thus giving rise to the exogenous echinococcus,[3] rather infrequent in man but more common in ruminants, pigs, and the horse; it occurs in the omentum, peritoneum, kidneys, mammary gland, and brain, exceptionally in the liver, but it never attains the enormous size sometimes seen in the endogenous variation.

Frequency.—Of 10,996,039 swine slaughtered under the U. S. Bureau of Animal Industry inspection during three months (September to November, inclusive, 1924) 2045 (or 1.86 per 10,000) showed hydatids in the liver. This would indicate that in certain rural localities, indigenous cases have probably occurred in man which have escaped attention. Several years ago Somer collated 100 cases in man for the United States and 12 cases for Canada, but as 33 of the United States cases were reported for New York alone, these statistics must surely cover only a percentage of the actual cases; they further show quite a percentage as having been found in foreigners, and as probably many, if not most of these latter brought their infection with them to this country, the figures can hardly be taken as representing American conditions. We may expect cases in rural and village districts in which the "country slaughter-house" flourishes. In Manitoba, the infection has been reported as common as among the Icelanders. Of the English-speaking countries, Australia has presented the highest figures; the province of Victoria, for instance, was reported to have 3 per 1000 mortality from hydatids and 1 case of echinococcus for every 175 hospital patients. The estimate of 400 deaths per year for England is very difficult to accept, especially in view of the comparatively few articles on this disease in English medical journals, but Huber quotes Murchison as reporting about 1.5 per cent. infection in his postmortem examinations. In certain parts of Continental Europe, echinococcus disease is not uncommon; thus Madelung reported for Rostock 1 case per 1056 inhabitants; from 1861 to 1883, Rostock also showed 25 postmortem cases in 1026 autopsies, or 2.43 per cent.; and certain slaughter-house statistics for entire Germany give an average of 10.39 per cent. for cattle, 9.83 per cent. for sheep, and 6.47 per cent. for hogs.

Iceland has been recognized as the classical echinococcus land, but

[1] Some acephalocysts are *Cysticercus*.
[2] *E. altriciparіens; E. hominis endogena; E. hydatidosus.*
[3] *E. granulosus; E. veterinorum; E. exogena; E. scoleciparіens.*

some of the published estimates must be taken with reserve and more recent reports indicate that the disease has become less common. The more conservative statistics give the infection as from 1 in 43 to 1 in 63 of the inhabitants, and Krabbe reported the adult worm in 25 per cent. of the dogs. Hydatids seem to be more common in females than in males, but some statistics give them as more common in males, and according to Meisser, they occur more commonly in patients from twenty-one to thirty years of age (about 30.8 per cent. of the cases collected).

The parasite is most commonly located in the liver. Thus of 1806 organ-infections, the following organs were the most frequently affected: Liver (1011), lung (147), and kidney (126); the parasite can, however, develop in any portion of the body.

Duration.—The growth of the echinococcus is very slow; according to Leuckart's experiments on swine, it takes five months for the cyst to reach a diameter of 15 to 20 mm. If scolices are fed to dogs, the development of the adult worm is also slow; about four to twelve weeks may be required for the worm to reach the gravid stage. How long a hydatid cyst might live in man is an open question; it has been stated that 50 per cent. of the infections are fatal within five years, but as many cases are doubtless not diagnosed, statistics on this point are always open to some question. Authority exists for cases in man of two to eight years' duration and even longer.

Symptoms.—The symptoms of echinococcus disease are practically those of a slowly growing tumor, which may attain 22 to 32 pounds in weight and cause different symptoms according to its location. In some cases the worm may die, the parasite then collapses, and the cyst becomes gelatinous and thick; the heads, or at least the hooks, may be found in the altered, thick, opaque contents. In some cases the cyst may suppurate. The hydatids are occasionally discharged through various channels (bile ducts, lungs, in urine, etc.). Urticaria may follow the rupture or puncture of the cyst admitting the echinococcus fluid into the body cavity, but it is said to occur with apparently uninjured cysts.

Diagnosis.—In many, but not all, cases, the so-called hydatid thrill or fremitus is felt on percussion, resembling the quivering of jelly. Deeply seated echinococci give an elastic feeling, superficial parasites a fluctuation. Positive diagnosis may be made microscopically by finding the hooks or heads in case of discharge, or in the aspirated fluid; exploratory puncture may result in dangerous sequelæ (hydatid intoxication, secondary echinococcosis, suppuration) and is therefore practised less frequently; presumptive diagnosis may be made by finding sugar in the aspirated fluid. As the roentgen-ray does not pass through hydatids, an examination by this method is of aid. The multilocular echinococcus is usually in the liver and accompanied by a chronic icterus.

Serodiagnosis seems to be increasing in value and exactness for at least the majority of patients with liver *Echinococcus* show specific antibodies in the blood which can be discovered by the complement-fixation test more delicately than by the precipitin method; some cases, especially when the cyst has suppurated, are negative. As an antigen, an alcoholic extract of the scolices (Patterson and Williams, 1924) is reported as stable

up to 15 months, and appears therefore of more routine value than the fresh hydatid fluid. It is needless to emphasize the point that this test is to be made by specially trained persons. Gasbarrini (1919) reports positive *dermal reaction*, in 11 out of 12 cases, upon injecting into the skin 0.5 cm. of bovine hydatid fluid (filtered; 1 drop of phenol to 20 cc.; then placed on ice); in three to twelve hours rusty, reddish, oval, spots with local œdema and local rise of temperature appeared.

Treatment.—Echinococcus infection is a surgical disease and only surgical interference is capable of curing it. Several authors refer to "boldly incising the cyst," but attention may be directed to the fact that by opening the external cyst (namely, the surrounding cyst which is furnished by the host) very cautiously, the inner cyst (namely, the parasite itself) can be taken out entire; to do this the external cyst should be raised at a convenient point, leaving a small space between it and the inner cyst. As hydatids can be obtained from the liver of hogs (at slaughter-houses), it is not difficult for surgeons to obtain a practical familiarity with the parasite and its cyst prior to contemplated operation. Strictly aseptic tapping has been followed by recovery. In the event of suppuration the condition is treated as one of abscess.

Prevention.—Since this disease is transmitted from dogs to man, and since dogs obtain their infection more particularly from eating the infected organs of slaughtered sheep, cattle, and hogs, it is clear that any plan of prevention should follow two lines: *First* and most important, dogs should be kept away from slaughter-houses to prevent them from eating the organs rejected on account of hydatid infection; the rule that no dog which enters a slaughter-house or its refuse yard should ever be allowed to leave would, if carried out, save human life and much valuable live stock, but it is difficult of application. *Secondly*, whatever our affection may be for "Old Dog Tray," we should recall that he is a dog and not a human being; in his place he is useful, but out of his place he may be a very dangerous friend.

So far as can be judged from the federal meat inspection, hydatid disease is much more common than is generally supposed, and it would appear that in some sections of the country the parasite has developed to such an extent that local boards of health should institute measures for its control by placing the local slaughter-houses under sanitary supervision.

Sparganum mansoni (Cobbold, 1882) is the larval stage of *Diphyllobothrium mansoni* of dogs. The eggs are passed in the excreta of dogs and in twenty-one days develop a ciliated embryo; this swims around in water and enters small crustacea (*Cyclops leuckarti*) in which it develops to the procercoid stage; when the crustacea are swallowed by frogs, the procercoid develops in the abdominal cavity to the larval *Sparganum* stage; if this latter is fed to dogs, it develops to the adult *Diphyllobothrium* in fifteen days; but if the *Sparganum* is fed to mice, rats, guinea-pigs, rabbits or frogs, it passes through the abdominal wall and lodges in various organs. As human flesh is not normally eaten by dogs, it is assumed that man is an accidental host. The *Sparganum* stage has been reported for man in various parts of the body, as subcutaneous, subperitoneal, pleural

cavity, ureters, subconjunctiva, etc., and in Japan, Indo-China, Australia, and Texas; presumably its distribution is much more extensive. In man the parasite may measure 8 to 36 cm. in length by 0.1 to 12 mm. in breadth and 0.5 to 1.75 mm. in thickness; it is flat and unsegmented. The same *Sparganum* is reported for monkeys, hogs, cats, boars, chickens, ducks, and snakes.

Surgical treatment should be used in superficial swellings, while in urethral cases the worm should be extracted while the patient is in a warm bath, the parasite being slowly drawn out or wound around a stick under water. It might perhaps be well to give the parasite a hypodermic injection of morphine shortly before pulling it out.

Sparganum baxteri Sambon, 1907 *d*, is reported as indistinguishable morphologically from *S. mansoni*. It was found in an abscess on the thigh of a Massi in German East Africa. Similar parasites were found in the body cavity of an African snake (*Bitis nasicornis*).

Sparganum proliferum[1] (Ijima, 1905) is a peculiar larval cestode first reported for Japan. It occurred in the subcutaneous tissue, especially of the leg, and produced acne-like swelling and a condition somewhat similar to elephantiasis. The worms measure 1 to 12 mm. long by 2.5 mm. in breadth, and possess the peculiarity of reproducing by budding. Adults and life history are unknown.

One case, of twenty-six years' standing and finally fatal, occurred in Florida. Upon autopsy the cadaver would have appeared emaciated had it not been for the enormous number of worms that filled the fat spaces so that the body had the appearance of being well nourished. The infection was almost generalized, extending even to the brain. The parasites reproduced in the larval stage by budding. So far as can be foreseen at present, the infection *appears* to be theoretically fatal.

ROUNDWORM INFECTION—NEMATHELMINTHES

The roundworms are divided into three major groups (see key, p. 499 namely, the *Eunematoda*, the *Gordiacea*, and the *Acanthocephala*. Of these, the nematodes are by far the most important, while the horse-hair worms and the thorn-headed worms are of secondary importance in human medicine. For practical reasons they are arranged in this article according to the part of the body they inhabit instead of according to their zoölogical arrangement.

INTESTINAL ROUNDWORMS

Uncinariasis[2] **or Hookworm Disease.—Geographical Distribution.**[3]—Uncinariasis encircles the globe in the tropical and subtropical belt,

[1] Synonyms.—*Plerocercoides prolifer; Plerocercus prolifer.* For detailed discussion, see Stiles, 1908 *c*, *Bulletin* 40, Hygienic Laboratory.

[2] Synonyms.—Anchylostomiasis; ankylostomiasis; brickmakers' anemia; dirt eating (in part); dochmiosis; Egyptian chlorosis; geophagia (in part); malarial anemia (in part); malnutrition (in part); miner's anemia; miners' cachexia; negro consumption; St. Gothard tunnel disease; tropical chlorosis; tunnel anemia; tunnel disease.

For literature on this disease, apply to the Rockefeller Foundation (New York), to the U. S. Public Health Service (Washington, D. C.), or to the State Board of Health of any Southern State from Virginia to Texas. These publications, profusely illustrated, are distributed *gratis* and should be in the library of every Southern physician.

[3] See *Publication No.* 6, Rockefeller Sanitary Commission, 1911.

diminishing in frequency in the temperate climates, but occurring locally in mines as far north as Great Britain, Holland, and Germany in Europe; in North America the endemic infestation stops about at the Potomac River, although carriers are found in practically every State in the United States in which detailed fecal examination has been made.

Fig. 81

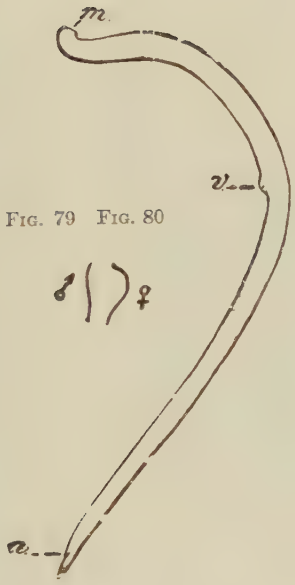
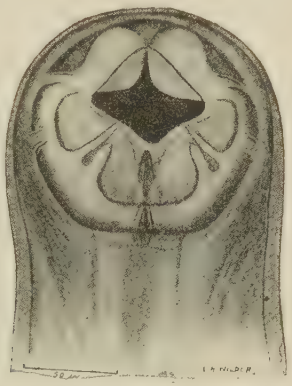


Fig. 79 Fig. 80

Fig. 82



Head, greatly magnified. We are looking directly into the mouth and see (above) the two semilunes or "jaws," and in the middle of the picture a hollow tooth, somewhat similar to the poison fang of a snake. (Stiles.)

Fig. 83

A side view of the head, greatly magnified and showing the mouth cavity (the very black portion), into which extend the prominent fang-like tooth and the sharp lancets. (Stiles.)

Fig. 79.—New World male hookworm. Natural size. (Stiles.)

Fig. 80.—New World female hookworm. Natural size. (Stiles.)

Fig. 81.—The same, enlarged to show the position of the anus (*a*) and the vulva (*v*). (Stiles.)

Zoölogical Distribution.—For practical purposes, hookworm disease in man is in general generically identical with, but specifically distinct from hookworm disease in dogs, cats, and hogs; but, academically, certain hookworm infections reported for cats, dogs, foxes, swine, apes, and even the rhinoceros, are specifically identical with hookworm infections of man.

The Parasites.—Most cases of hookworm disease in man are due to either one or both of two distinct species of parasites (belonging to the superfamily *Strongyloidea*), namely, the New World hookworm (*Necator americanus*) and the Old World hookworm (*Ancylostoma duodenale*). Other species (*A. braziliense, A. caninum, A. ceylanicum, A. incertum*) occasionally reported for man are of relatively very secondary importance.

The New World hookworm, *Necator americanus*[1] (Stiles, 1902), is the common hookworm of the American continent and adjacent islands, but it has been introduced into Italy, and doubtless also into Spain. It has been reported for Africa, Guam, and elsewhere and is now known to have a very wide distribution. It was doubtless introduced into the Americas from Africa. The same parasite is reported for the gorilla, chimpanzee, *Cercopithecus patas*, hog, dog, and rhinoceros; its occurrence in dogs seems to be exceptional. This cylindrical worm is 7 to 11 mm.

Fig. 84

Fig. 85

Fig. 86

Fig. 87

Figs. 84 and 85.—A hookworm egg in process of development. At first this egg contains only 1 cell, which later divides into 2 cells, each of which divides, thus forming 4 cells; these cells keep on dividing until, sometimes by the end of eight hours, a roundworm (Fig. 86) is formed. (Stiles.)

Fig. 86.—This shows the young worm a short time after it escapes from the eggshell. The bottle-shaped structure at the blunt end is the œsophagus, or gullet, and the darker organ following this is the intestine. This worm crawls or is scattered around on the ground. It feeds for about eight days or more, according to conditions, storing up food and growing; during this process it sheds its skin twice, much like a snake. (Stiles.)

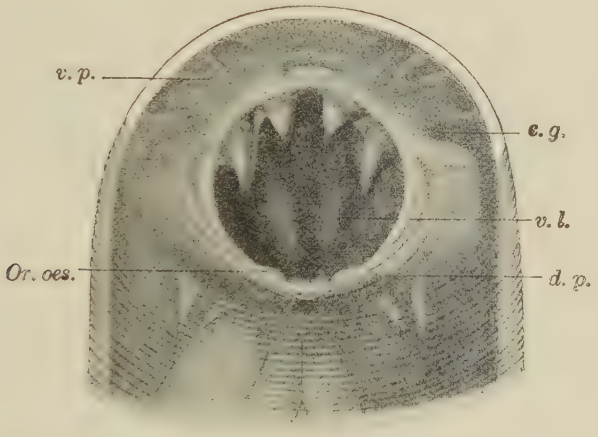
Fig. 87.—This represents the worm about to shed its skin the second time; the worm remains encysted, as shown, in this skin, or it may escape from the skin; it now no longer takes food until it enters man. It may live just so long (one to six months, more or less) as it can live on the food which it has already eaten. If it becomes completely dried it dies; therefore it cannot be blown around alive in the air as dust; prolonged solid freezing kills it. When partially dry it is quiet, but it is very active when wet, as in dew. It can wriggle up a surface which is moist. The worm may be swallowed but more generally it enters through the skin. (Stiles.)

[1] Synonyms.—*Uncinaria americana; Ankylostomum americanum; Uncinaria hominis* 1904 in part; *Necator africanus* Harris, 1910 (not Looss); *N. argentatus* Parodi, 1920.

long and possesses a ventral pair of semilunes or "jaws," a prominent dorso-median buccal tooth, and four buccal lancets; in the male, the dorso-median (No. 7) ray of the bursa divides at the base and each branch possesses two tips. In the female the vulva is preëquatorial. The eggs are thin-shelled, 64 to 72 μ long by 36 to 40 μ broad; they are oval with somewhat bluntly rounded poles.

The Old World hookworm, *Ancylostoma duodenale*[1] Dubini, 1843, is the common hookworm of Egypt and has a wide distribution in Europe, Asia, Africa, and Australia; it has been introduced to some extent into the Americas. Its measures 8 to 18 mm. in length and possesses in its mouth 2 pairs of strong, curved, ventral teeth and 1 pair of knob-like dorsal points; the dorso-median tooth of the buccal capsule is nil or practically so; a pair of ventral lancets is present in the buccal cavity. In the male, the dorsal ray of the bursa is divided two-thirds its length from

FIG. 88



Dorsal view of the Old World hookworm: *c. g.*, opening of cephalic gland; *Or. oes.*, entrance to œsophagus; *v. l.*, ventral lancet; *d, p, v, p.*, dorsal and ventral papillæ; note also the four teeth. Greatly enlarged. (Looss.)

the base and each branch is subdivided into three tips. In the female, the vulva is postequatorial. The eggs measure 52 to 61 μ long by 32 to 38 μ broad; they are oval with very bluntly rounded poles.

These parasites inhabit the small intestine, especially the jejunum and ileum but also the duodenum, and occasionally the stomach and the appendix.

This species appears to be practically confined to man; its reported presence in cats in the United States seems to be based upon an error of identification; but it has been transmitted experimentally to kittens and puppies; experiments to transmit it to old dogs, to rats, mice, guinea-pigs, rabbits, swine, and dogs, are reported as negative.

[1] SYNONYMS.—*Anchylostoma duodenale; Dochmius duodenalis; Anchilostoma duodenale; Uncinaria duodenalis; Ankylostoma duodenale; Ankylostomum duodenale; Uncinaria hominis*, 1904, in part.

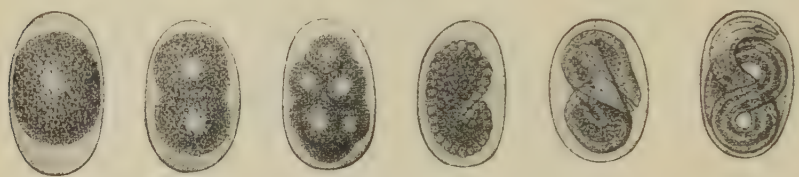
A. braziliense Gomez de Faria, 1910, occurs in dogs, cats, and man. Its mouth shows ventrally one pair of large teeth and a more median pair of exceedingly minute teeth. The type locality is Brazil, and while the same species is reported for Asia and Africa, the Old World specimens seem to be, at least usually, more of the *A. ceylanicum* type. Some authors consider the two forms specifically identical, others consider them distinct.

A. ceylanicum Looss, 1911, occurs in dogs, cats, and man; it is quite possibly an Old World geographic subspecies of *A. braziliense*. The mouth shows ventrally one pair of large teeth and a more median pair of very small teeth.

A. caninum Ercolani, 1859, the common hookworm of dogs, has been reported occasionally, though rarely, for man.

A. incertum Sonsino, 1896, was originally reported for horses, but it is now considered that the specimens came from man and were, in reality, *A. duodenale*.

FIG. 89



Six stages in the embryonic development of Old World hookworm; *a-c*, are the stages found in fresh feces. × 336. (Looss.)

Source of Infection.—The females oviposit in the intestine of the host; but the eggs do not develop until after they escape with the feces; then they develop within twenty-four hours or more, according to conditions of heat (especially 25° to 30° C.), moisture and amount of oxygen, a rhabditiform embryo which escapes from the eggshell, feeds and undergoes ecdysis (shedding of skin) after about forty-eight to seventy-two hours; a second ecdysis which occurs within about five to nine days changes the worm to the infecting stage—the so-called "encysted or strongyloid larva;" from this point the worm takes no more food until it reaches man. Infection takes place in two different ways: (1) It has been experimentally demonstrated, first by Looss, that hookworm larvæ pass through the skin, reach the circulatory system, pass with the blood through the heart to the lungs, from the lungs to the air passages, up to the larynx, down the œsophagus to the stomach and then to the small intestine. This is the common method by which hookworms gain access to the system, especially in warm weather (as above 25° C.). (2) A second method of infection has been experimentally demonstrated, *i. e.*, through the mouth, either with contaminated food or water or from earth containing the hookworm larvæ and, clinging to the hand, especially in cooler weather (as below 20° C.) when the worms are less active.

The view advanced that the free embryos develop into free adults, the progeny of which become parasitic, is not in harmony with what is

otherwise known of this group of worms and it may safely be eliminated from consideration.

Frequency. -The spread of uncinariasis is inconsistent with a proper sewage system, cold weather or dry conditions. Accordingly, in general terms, it is more common in moist localities than in dry, more common in warm countries than in cold, and more common in rural districts than in cities. Although it is one of the worst scourges of the tropics, even there its frequency can be decreased by a proper disposal of feces, for fortunately the more important specific infections in man are not common in the domesticated animals.

It is to no little extent an occupational disease, for it is more common among people who come into direct contact with damp earth, as farmers, miners, tunnel-diggers, and people (as children) who go bare-footed, than it is among persons of other occupations and those who wear shoes.

Many authors report that it is more common among men than among women and children, others that it is more common and more severe in children and women than in adult males. It is not difficult to harmonize these divergent statements. Physicians reporting for mining districts would, in general, find more cases among the miners (namely, among men), for the infection here occurs chiefly "underground," while the homes in many mining districts are provided with sewage or proper privies and the miners' families are thus more or less protected from infection. Further, many authors have reported upon cases which came to them for diagnosis and treatment, while other writers have gone to the families in order to find the cases; hence the conditions covered by the latter reports represent more exactly the natural conditions in the rural districts visited. Again, in rural districts containing more children than adult males, as in the localities in question, under conditions favorable to infection there would naturally be more cases among the children; furthermore, the children and women were in some instances following a life more conducive to infection (namely, staying near the house, which by local custom may be an area of concentrated infection, more than were the men), and infection would therefore be expected to be more common among the former. In general, frequency varies with the degree of exposure to infection, but certain laboratory experiments and clinical observations seem to indicate that it is not impossible that a difference in intensity and frequency of infection may perhaps be found in different classes even when exposed to apparently the same chances for infection.

Ashford, King, and Gutierrez (1904), in their splendid "Report on Anemia in Porto Rico," found more cases (1027 of 5490) between the ages of five and nine years than at any other five-year period; of the same 5490 patients, 3259, or 59.34 per cent., were males, and 2131, or 40.66 per cent., were females.

In the districts visited by the writer, uncinariasis is preëminently a disease of the piney wood and sand localities, occurring less in clay regions. However, this distribution was not found in Porto Rico. Some physicians in the South have confirmed the author's findings in this respect while others have obtained different results, the explanation for which is not entirely clear at present. There is evidently some factor which has

escaped attention, and which will doubtless harmonize the divergent reports. Possibly Nicholson and Rankin (1904) have given the correct clue when they state that it is not so much a question of the *sandy* nature of the soil as it is a question of *fine* soil which by its ability to hold moisture offers the most favorable conditions for development. Presumably, also, the different chemical composition (as salt-content) and the pH of the soils have contributed to seemingly contradictory findings. Further, trees naturally protect the young worms, to some extent, against the drying effects of the sun. A certain seasonal periodicity is shown insofar that new infection decreases in cold and very dry seasons, but increases in warm and moist seasons. Uncinariasis is more common and more severe among the poor than among the well-to-do, and more common among people who live in conditions of filth than among those who live in better hygienic conditions; neither individual wealth nor individual refinement is a guarantee against infection, but rather this is to be sought in *community* and family sanitation.

Statistics.—The statistics of hookworm infection are not on a uniform basis; some figures include both carriers and patients; others only suspects, or only patients, or selected, or unselected cases. Too much weight is not to be attached to this point. The chief value of the statistics is to show the wide distribution of the infection, for with a decrease of infection percentages there is decrease in potentially direct and indirect morbidity. The most extensive statistics are those of the Rockefeller Foundation, which reports that of 1,413,000 persons examined, 1910 to 1923 inclusive, in our Southern States, 36.7 per cent. showed infection; (about 1908, the present author estimated the average rural infection as about 30 per cent.); of 89,857 school children in 81 of the 422 Southern counties surveyed in 1910–1915, 51 per cent. showed infection; in these same 81 counties, surveyed in 1920–1923 (after hookworm campaigns), of 44,090 school children examined, 27.8 per cent. showed infection. In the West Indies, the infection was 66 per cent.; in Central America 62.7 per cent.; in South America 81.4 per cent.; in the East, 64.9 per cent.

Experience shows that the infection, either carriers or patients, varies in different schools and in different countries from 100 per cent. down to 1 per cent. or less. Accordingly, the individual reports are subject to great variation and this has been prominently reflected in opinions expressed by different authors.

Pathology.—Aside from the anemic conditions, attention may be directed to the intestinal tract. The stomach is frequently dilated and exhibits a chronic catarrh. One observer speaks of attacks of acute dilatation, especially in children. The small intestines, especially the jejunum and ileum, show a diffuse catarrh of variable severity and the bites made by the worms; hemorrhages may be present or absent; there may be a large spot of hemorrhagic infiltration with a worm hanging from its centre; there is a chronic interstitial inflammation; Ashford, King, and Gutierrez report the intestinal wall as very much thinned but several authors report it as very much thickened; constrictions have been reported in South American literature.

The parasites injure in different ways, but evidence seems to be accu-

mulated in support of the view that their toxic effect is more serious than generally admitted. Loeb and Allen J. Smith showed that hookworms produce a substance which inhibits the coagulation of the blood. It is not excluded that the condition of the intestines and their contents, due directly or indirectly to the parasites, has been underestimated in respect to its role in this disease.

Symptoms.—Cases may be divided into carriers (*light*) and patients (*medium*, and *severe* infections). Under the *light* infections may be included those patients who show eggs in the feces upon microscopic examination, but who do not exhibit any or sufficiently marked symptoms to attract special attention. These cases, known as "*carriers*," are numerous and are important in that they are capable of keeping a region infected and thus giving rise to severe cases; hence from a prophylactic standpoint, they should always be taken into consideration (chiefly through sanitation). Furthermore, despite the assumed lack of symptoms, indications are not lacking that even "carriers" may be influenced to a slight degree in respect to their weight, their mentality, and other factors. Under *medium* cases may be included those persons who show a definite anemia, while other symptoms, mentioned below, develop to an extent which attracts sufficient attention to bring the patient under medical treatment; a physician in the infected district should immediately suspect uncinariasis but the Northern physician might not be so promptly led to this diagnosis. Under *severe* cases may be classified the typical or near dirt-eaters who present a clinical picture which even the laity in the South recognize on sight.

These three phases grade imperceptibility from the lightest to the most severe.

General Development.—If infection occurs before puberty it is likely to retard development both physical and mental. A boy or girl of twelve to fourteen years may appear to be eight to ten and one of eighteen to twenty-two may appear to be not over twelve to sixteen.

Skin.—The skin may be waxy white to dirty yellow, tallow or tan, the color being a general superficial, but not in all cases exact, indication of the degree of anemia. It becomes dry and parchment-like, perspiration being more or less completely suppressed. Petechiæ may be observed in older cases. Pruritus may be noticed more or less frequently. Atrophy of the skin is seen in chronic cases.

Ground-itch.—As Bently (1902 *a*) pointed out, it is very common to find a history of ground-itch in hookworm districts. Of 4741 Porto Rican patients questioned by Ashford, King, and Gutierrez on this point, 4654 or over 98 per cent. gave a history of "mazamorro," as the dermatitis is called by the natives. "New Sump bunches" in the Cornwall miners is reported by Boycott and Haldane. In our Southern States ground-itch is exceedingly common in some districts, especially during wet weather. The present evidence clearly shows that this rapidly developing condition (characterized by a few itching papules to a severe dermatitis, found more particularly in bare-footed people, between the toes especially and on the sides and top of the foot, and in some cases on the buttocks or other portions of the body) is the initial symptom of

uncinariasis, due to the penetration of the larvæ into the skin, and doubtless accompanied in many cases by some bacterial infection. Not *all* cases of this affection are due to uncinariasis, for *Strongyloides* larvæ, also, may enter the skin and produce a "ground itch;" our observations are to the effect that ground-itch (also known as foot-itch, toe-itch, wet-weather-itch, dew-itch, etc.) includes at least three different conditions.

Hair.—While the hair on the head may be normally developed, it is likely to be dry and harsh, and there may be a marked scarcity or absence of hair on the pubes, in the armpits, and on other parts of the body, in patients who become infected before puberty.

Œdema.—Œdema of the face, feet, ankles, leg, scrotum, or entire body may occur. According to the Porto Rican (1904) statistics it was most frequent in patients with a hemoglobin of 20 to 48 per cent.

Wounds and Ulcers.—In a number of cases even slight lesions of the skin heal slowly. In severe cases, ulcers (some of one to nine years' standing) are not uncommon; they are usually situated on the tibia or the foot; in some instances they heal promptly after the worms are expelled from the intestine. The question arises whether some cases of so-called hookworm ulcer are in reality "tropical ulcers," and *vice versa*.

Head.—The face may show an anxious, stupid expression with chalky-white conjunctivæ. The pupils have a decided tendency to dilatation; the patient may show a blank stare; night-blindness is reported in a number of cases. The mucous membranes vary from a natural color to a white, corresponding more or less to the degree of anemia. Recurrent attacks of epistaxis have been observed. The tongue may show purplish smears on each side of the median line; pigmented spots and a partial denudation of the epithelium may be observed.

Neck.—Cervical pulsation, especially in severe cases, is very evident, often being visible from six to twelve feet from the patient.

Thorax.—In emaciated cases the ribs are of course very prominent. The infraspinatus muscles are frequently underdeveloped and the scapulæ may show a pronounced "winged" condition.

Abdomen.—A more or less prominent abdomen is rather common, known among the laity as "pot-belly," "buttermilk belly," or "shad-belly," and ascites may develop.

Digestive System.—Appetite: This may be light to ravenous; in late stages there may be complete anorexia. There is a marked tendency to an abnormal appetite for sour articles as pickles, or for salt, coffee, and buttermilk, or a perverted appetite for resin, charcoal, chalk, tobacco ashes, dried mortar, mud, clay, sand, gravel, shells, rotton wood, cloth, garments (the writer met one boy who had eaten three coats, thread by thread, within one year), paper, tobacco pipes, and even mice and young rats. Salivation is frequent. Flatulence and heart-burn are common; nausea is frequent and vomiting may occur. Pain and tenderness in the epigastrium are mentioned by nearly all observers; Ashford, King, and Gutierrez (1904) give it as "the most constant, most suggestive, and most clearly marked of all the symptoms of the digestive tract." Constipation is common, but diarrhœa may be present. The statements by authors

relative to the feces are very contradictory, which indicates that various conditions may occur. Ashford, King, and Gutierrez found blood macroscopically in only 6 cases, and blood and mucus in 5 cases, out of over 22,000 fecal examinations, statistics which are far below the conditions observed in the Gulf-Atlantic States by the writer. Leichtenstern suggested that the blood is more likely to appear during the period of copulation of the worms. In some cases blood may be absent, in other cases present, either macroscopically or microscopically, in the stools.

Circulatory System.—Heart: The apex beat is pronounced in the slight grades of the disease; in moderate grades it is often displaced downward and to the left; in marked grades, there is great reduction in the force of the apex beat, which is replaced by a wavy, indefinite pulsation or a tumultuous heaving of the whole precordium, and in these cases cyanosis, chiefly in the lips, is common; a presystolic thrill is not infrequent in moderate cases, more common in marked cases; in moderate cases, hypertrophy, especially of the left ventricle, causes an enlargement of the heart area; the murmurs are best heard in the third intercostal space; in moderate cases, hemic murmurs are almost always present (Ashford, King, and Gutierrez). Palpitation occurs early and is very prominent and constant. The *pulse* varies from 80 to 132, without any necessary relation to the temperature; in the later stages it becomes dicrotic, then weak and compressible, finally thready, irregular, and intermittent. Dyspnœa is very common, especially in the later stages.

Blood.—The anemia is pronounced and has been taken as basis for a number of the vernacular names of the disease. Ashford, King, and Gutierrez (1904) made a faithful study of the blood conditions. In one series of 540 persons, compared as to race, they found the average *hemoglobin* at over 45 per cent. in whites, over 44 per cent. in mulattoes, and over 49 per cent. in negroes. In a series of 577 persons compared, in reference to sex, the males showed an average of 41 per cent. hemoglobin; females, 48 per cent. Of one series of 579 cases, the hemoglobin upon later examination during treatment showed an increase in 371 cases from 1 to 71 per cent., average 21.34 per cent.; 7 cases neither gained nor lost; a weekly increase of 20 to 30 per cent. was not rare. During the disease, the hemoglobin may reach as low as 30 per cent. before much change in the reds is noticed; under treatment the reds usually increase more rapidly than the hemoglobin.

The *red* cells vary from 754,000 to normal or above, according to conditions; of 61 special cases, the average was 2,406,416; as the disease progresses, the cells become polychromatophilic and show poikilocytosis; under treatment the red cells increase very rapidly, reaching or exceeding normal sometimes before the hemoglobin. In 42 treated cases with a final average of 100 per cent. hemoglobin, the red cells averaged 5,624,197. *Leukocytosis* was not observed in Porto Rico; the majority of cases showed 5000 to 10,000 leukocytes, and in chronic cases of long-standing leukopenia was often found; the average white count of 61 cases was 8009 on admission. Leukocytosis was frequently found in hookworm cases at the Marine Hospital in Wilmington, N. C., but especially in children who had enlarged tonsils. The *eosinophiles* present special

interest: very severe chronic cases with poor resisting power and exhausted blood-making organs have little or no eosinophilia; a rise in eosinophiles is of good prognostic import; if very severe cases, presenting little or no eosinophilia, show a fall in the eosinophile count, the prognosis is not generally good; in general, good resistance to the toxin of hookworm is expressed by eosinophilia; the "special" cases gave an average of 10.8 per cent. before treatment, and 13.2 per cent. after treatment. In 29 cases, before treatment, the differential leukocyte count averaged as follows: Eosinophiles, 17.1 per cent.; polymorphonuclears, 54.5 per cent.; small lymphocytes, 16.3 per cent.; large lymphocytes, 8.6 per cent.; other leukocytes, 3.5 per cent.

Respiratory System.—The respiratory symptoms are not characteristic. A cough is likely to develop a few days after the ground-itch infection. Later, patients may complain of difficulty in breathing, especially after exertion.

Temperature.—This may be subnormal, normal, or reach 100° to 102° F. Fever at the onset is said to be a fairly constant symptom in Porto Rico. Some observers speak of a "hookworm fever."

Nervous System.—The effect upon the mental condition is marked; the infected children, of school age, are greatly handicapped by it in their studies; in severe cases, there is a noticeable delay in answering even simple questions and some of the patients are more or less stupid. From the pedagogic point of view, the hookworm inhibition to the mentality is probably the most important feature of the disease and deserves more general consideration; for instance, if a given "grade" or class in school is divided into a more advanced and a less advanced section, the majority of the hookworm cases will be found in the latter; many of the so-called "repeaters" (children who have to repeat their term in a given grade) in our Southern schools are hookworm patients who, after treatment, advance more rapidly. Mental lassitude, headache, and dizziness are frequent; the patients may be more timid and emotional than normal; the patellar reflex is diminished or suppressed; tingling and formication are common; insomnia or somnolence may be marked; dizziness is common, especially upon rising suddenly to the feet; joint-pains are frequent.

Muscular System.—The muscles are soft and flabby, and the patient is naturally weak; the "hookworm hand-grip" (with very briefly sustained hold) is usually rather pronounced; the patient tires easily, is obliged to rest after slight exertion and a feeling of lassitude is experienced which, in absence of severe symptoms, may seem unexplained; as a result, persons who are not acquainted with the true condition attribute it in the less evident cases to laziness, and there is no doubt that much of the alleged laziness in infected districts is the natural lassitude due to uncinariasis.

Urinary System.—The urine varies from 1.010 to 1.015 in specific gravity, is pale, neutral or alkaline, rarely acid, and is increased in amount.

Genital System.—In case of infection before puberty, delayed development may be very marked. Menstruation may be delayed several years beyond the normal and may be more or less irregular, or absent, especially in summer. A fecal examination for hookworm eggs should be made as

routine in all tropical and subtropical cases of delayed menses. Abortions and miscarriages are frequent. Sterility and impotence are common.

Lethality.—The writer cannot state the average lethality of untreated cases in the United States, but Ashford, King, and Gutierrez (1904) expressed the astounding—yet probably correct—opinion that 30 per cent. of the deaths in Porto Rico were due to uncinariasis. The Porto Rico Commission reported one series of 5490 treated cases with the following results: Cured 2244 cases, or 40.8 per cent.; practically cured, 377 cases, or 6.8 per cent.; improved, 1727 cases, or 31.4 per cent.; result not recorded 522 cases; never returned, 224 cases, and ceased to return, 283 cases, total 18 per cent.; unimproved, 86 cases; died, 27 cases, or 0.5 per cent. Sandwith (1894) stated that of the patients nominally under his care, 89.5 per cent. were cured or greatly relieved, 2.5 per cent. were not relieved 8 per cent. died.

So far as can be conservatively judged, the direct mortality of hookworm disease in the Gulf-Atlantic states is of very secondary importance when compared with the increased concurrent morbidity and indirect mortality, for this infection clearly reduces the powers of resistance to concurrent diseases.

Economic Importance.—A person who has not been in an uncinariasis district and who has not seen the way many of the people live, or rather exist, how they attempt to work, how little they accomplish, how the mental faculties are dulled, how backward the children are, how the much-criticised country school teachers are handicapped in their work, how exhausted the laborers become and what a change takes place in them during and after treatment, may find it difficult to grasp the full economic importance of this malady. As stated by the writer in 1902, it was "exceedingly difficult to escape the conclusion that in uncinariasis, caused by *Uncinaria americana*, we have a pathological basis as one of the most important factors in the inferior mental, physical, and financial condition of the poorer classes of the white population of the rural sand and piney-wood districts visited. This sounds like an extreme statement, but it is based upon extreme facts." The importance of this disease from the standpoint of public school work and citizenship has not yet been fully grasped by the average well-informed citizen. As observations in the United States have multiplied, what once seemed an extreme opinion rapidly became a very conservative view.

The importance of the disease in the cotton mills is not to be underestimated. The typical cotton mill "anemic" is a diagram of medium to severe uncinariasis. From a purely financial point of view, it would pay the Southern cotton mills to compel all candidates for positions to submit to examination for diagnosis, and, if infected , to make treatment a condition for employment. Whether the American mines will experience a repetition of the expensive history European mines have had from hookworm disease, will depend upon the sanitary regulations they enforce.

Diagnosis.—In severe cases, a diagnosis upon symptoms can be made with a very high probability of correctness by anyone familiar with the disease. A positive diagnosis can be made in either of two ways: (1) Examine the feces microscopically to find the eggs; or (2) give an

anthelmintic experimentally and examine the stools for the adult worms. Eggs appear in the feces forty-five to seventy-four days after the patient becomes infected.

Treatment.—Treatment of hookworm disease is to be considered from two very different points of view, namely, (*a*) the viewpoint of the clinician who deals with individual private or hospital patients, to whom it is possible to give individual study and attention, and (*b*) the viewpoint of the field worker who considers the district population (or other mass unit) as a whole and who must make his available funds do as much total good as possible to the community.

Further, also, a routine which may be entirely justified in one island or country, where life is more primitive, may not appeal favorably to persons who are dealing with a higher type of civilization. If these comparisons are not taken into consideration, it may be difficult to understand some of the recent hookworm literature.

From the very nature of things, a field worker who treats *en masse*, and occasionally even by proxy, must of necessity assume risks which the conservative clinician avoids; but the field worker will be blamed only by the person who does not balance the enormous total improvement, with its potential reduction in general morbidity, against a few accidents which might be avoided if every sparsely settled or economically poor locality could afford a finely appointed hospital, or if every semi-civilized patient could have his private physician, together with day and night nurses.

Local procedure must be determined by local conditions of finance, degree of infection, sociology, etc. Procedures possible in a home or a hospital in a medical centre are not always feasible in field work; and conversely, procedures justified in field work are not always justified in a medical centre.

The present author's experience is, however, not in harmony with the view that hookworm disease reduces itself, either as a clinical or as a public health problem, to a practical proposition of mass treatment of children of school age once every year or two or that it is of importance only as a problem of childhood, or that it takes a minimum of 40 or 50 hookworms to produce symptoms regardless of age, sex, race, or condition of the host.

Unless the question as to whether treatment is worth while be considered from two very different viewpoints, namely, worth while as applied to an individual person who is sick or worth while as applied to a campaign, not only will the campaigns fall into disrepute but individual patients will not receive the attention they deserve.

The writer holds to the view he expressed nearly twenty years ago, that the control of hookworm disease should consist of about 10 per cent. of treatment (primarily for patients) and about 90 per cent. sanitation (primarily for carriers); but where sanitation presents almost insurmountable difficulties (as in many tropical countries) it is well to treat carriers when occasion presents (as in mass treatment in heavily infested areas, and then even without preliminary microscopic examination). In private practice, however, he considers standard treatment (as com-

pared with therapeutic diagnosis) without preliminary microscopic diagnosis as justified only when the symptomatic diagnosis is made by a person who has practical familiarity with the disease.

The present discussion is intended primarily for the individual case, not for campaign work. Accordingly, the questions of worm counts, cost per dose of drug, etc., are not considered.

In selecting a drug for use in hookworm disease, several factors come into consideration: (*a*) Anthelmintics are of necessity poisons, otherwise they would not affect the worms; accordingly, it is desirable to select a drug which under all circumstances (regardless of alcoholism, concurrent disease, pregnancy, diet, etc.) has a considerable margin of safety (between the therapeutic and the toxic dose). (*b*) The average hookworm patient under treatment is not inclined to persist to a cure; accordingly, it is important to use a drug with a high degree of efficiency so that the number of administrations can be reduced to a minimum. (*c*) The more the routine of treatment interferes with the comfort, diet, and work of the patient, the less likely he is to carry out directions; accordingly, it is desirable to give consideration to this point. (*d*) As the average patient is financially at a disadvantage, it is necessary to consider economy as respects repeated visits by the clinician and frequent or prolonged visits to a hospital. (*e*) As the average case is not provident and does not see the value of a complete cure, treatment must be reduced in time so far as practicable. (*f*) Treatment results in such prompt improvement that the average patient, feeling so much better than he was, thinks he is cured before he really is. (*g*) As the average person does not appreciate that he is a potential danger to himself and to his family, his treatment is a subjective matter, rarely with altruistic motives. (*h*) Many hookworm families are too ignorant to be trusted to graduate the doses according to directions, and they sometimes find it easier to give all members (children and adults) the same dose; accordingly, it is often more satisfactory for the physician or the nurse to administer the drug.

These factors combine to make the selection of the drug a more complicated matter than if one could be administered "one teaspoonful, t.i.d., before meals." As none of the 70 drugs thus far tried is known to meet all of these conditions, there is no perfect hookworm remedy. But all things considered, chemically pure carbon tetrachloride probably fulfils as many desiderata as does any of the other remedies extensively used: the margin of safety is high (except in cases of alcoholism and of concurrent hepatic disease); it is very efficient, so that a single dose expels a high percentage of the worms; it interferes very little with comfort and diet; it can be administered at the physician's office and the patient usually permitted to return home. Despite these advantages, however, some excellent clinicians who have tried it have rejected it in favor of other drugs. Oil of chenopodium presents about the same degree of efficiency, but complaint has arisen as to its lack of standardization, and its dangers, as in pregnancy. Thymol, for some years the drug of choice, still has its advocates. Male fern has been used extensively, as have beta-naphthol and also chloroform. Mhaskar (1924), after very extensive study in India, considers beta-naphthol the drug of choice.

If the clinician is in control of the situation, as in a hospital or other institution, and does not have to reduce the treatments to a minimum, he may still prefer the less efficient standard thymol treatment in special cases, rather than the more efficient carbon tetrachloride or the oil of chenopodium. The variations in technique in administering the different drugs are numerous, but the following methods have been extensively used:

Carbon Tetrachloride.—One great advantage of the drug is that it can be given without interfering to any extent with the diet (but some clinicians prefer to omit breakfast on day of treatment). Doses totaling as high as 10 to 50 cc. have been administered, but an adult dose of 3 cc. is now usually considered the maximum necessary or justified; children receive a maximum of 2 minims for each year of age. The total dose (adult maximum 3 cc.) is given at one time, in water or in freshly filled gelatine capsule, and followed after two hours by magnesium sulphate.

Patients frequently experience eructation with a taste resembling that of boiled cabbage, also headaches, dizziness, and occasionally nausea and somnolence. Experimental studies on dogs show that the drug produces transient lesions of fatty degeneration of the liver and of the kidneys, which are at a maximum thirty-six to forty-eight hours after drug administration and of which the repair is rapid, usually being completed in two to three weeks; the severity of the lesions appears to vary in inverse ratio to the age of the animal, and the necrosis is in proportion to size of dose. The drug is contraindicated in cases of alcoholism, hepatic, or renal disease. It has been administered in many cases of pregnancy without producing abortion, but at least one case of abortion in experimental dogs is recorded. If food is taken immediately before or after drug administration, constipation may result and the absorption of the drug thus be increased. Preceding carbon tetrachloride administration, mixed diets and high-protein diets appear more or less protective; starvation is harmful; all-fat diets are conducive to maximal injury of liver parenchyma (Davis, 1924, 613). Several deaths have been reported.

If a second treatment be given, this should be not less than three weeks after the first dose.

Oil of Chenopodium.—This drug is efficient against hookworms and *Ascaris*, and is reported as giving good results in amœbic dysentery. In the open market it is, however, not uniform. Of the numerous variations in technique, Darling and Smillie (1921, 32) advise the following for dispensary and hospital conditions: (1) 8 P.M., saline purge; (2) 7 A.M., (no breakfast) a single dose (adult) of 2 c.c. (graded dosage for children) of oil of chenopodium (in capsule); (3) 9 A.M., saline purge (some authors prefer castor oil). Treatment may be repeated after twelve days. The graded doses for children vary considerably. For instance, Ceylon doses are: apparent age two to twelve years, 1 minim for each year, minus 1 minim; thirteen to fourteen years, 13 minims; fifteen to sixteen years, 16 minims; seventeen to eighteen years, 20 minims; nineteen to twenty years, 24 minims. Oil is dropped from a dropping bottle into simple sugar syrup.

Children are more susceptible to chenopodium than are adults; for instance, of two groups of fatal cases totalling 17 deaths, 16 were in children.

Thymol.—The more conservative procedure is as follows: As the parasites are more or less protected by the mucus and food in the intestine, this is removed by administering magnesium or sodium sulphate (with *abundant* water), or other cathartic, the evening before the anthelmintic is taken. Early the next morning (no breakfast is allowed), say at six o'clock, give (adult dose) 2 gm. (30 gr.) of finely powdered thymol in capsules; at eight o'clock, repeat this dose; at ten, administer another dose of salts. The size of the dose should be modified according to the age or the condition of the patient. Ashford, King, and Gutierrez, on the basis of an experience with 12,330 doses, state that in general a total in one day, of 0.5 gm. (7.5 gr.) may be given with good results to children under five years; 1 gm. (15 gr.) between five and ten years; 2 gm. (30 gr.) between ten and fifteen years; 3 gm. (45 gr.) between fifteen and twenty years; 4 gm. (60 gr.) between twenty and sixty years; and 2 or 3 gm. (30 to 45 gr.) above sixty years. Certain conditions, as great debility, very old age, pregnancy, advanced cardiac or other organic disease, a tendency to vomit, anasarca, chronic diarrhœa, and dysentery are unfavorable to the administration of thymol. This medication is carried on one day per week until the patient is cured. The present writer adopts the Porto Rican doses as routine, but he prefers as a precautionary measure to divide the total day's dose of thymol into three portions, administered at 6, 7, and 8 A.M. respectively, salts at 10 A.M. At the Marine Hospital, Wilmington, N. C., the patient is permitted coffee about 9.30 and again about 10.30. The thymol is withheld after the first or second divided dose if untoward symptoms are noticed. Thymol treatment is repeated one day per week until microscopic examination of the stools, six or seven days after treatment, is negative for ova.

It is in the interest of safety not to allow or give by mouth any alcohol, oil, or other solvents of thymol on the day of treatment.

Many authors warn about the ill effects of thymol. The Porto Rican Commission after administering 12,330 doses *seems* to incline to the view that these warnings have been exaggerated and states that, "under certain precautions," they "came to know that thymol was an exceedingly inoffensive drug." Still, they warn of certain ill effects in some cases (especially with chronic enterocolitis, œdematous patients, etc.). Some of the investigators in India concur in the view that the dangers of thymol have been over-emphasized. Nichol (1911) refers to the "serious disturbance" caused by doses totaling 90 grains per day; these observations are to the effect that the drug acts chiefly on the nerve centres; at first it stimulates, the patient is inclined to talk and laugh, the face flushes, pulse quickens, soon there follow dizziness, drowsiness, sleepiness, the pulse become quick and compressible, syncope appears; in more serious thymol poisoning, somnolence passes into coma and death may ensue. In the United States there have been at least 12 deaths, due chiefly to following thymol with oil, or to carelessness in the precautions; 1 death was apparently due to the Epsom salts in a case with a severe kidney

complication. Mhaskar (1924), whose (Indian) patients obviously show less severe symptoms than our Southern whites, administers 50 gr. (adults maximum dose for day) of thymol, mixed with 25 gr. of magnesium carbonate, in a single portion with a little water, and without pre- or after-purge. But of one series of 1606 cases, 10 per cent. showed distinct toxic symptoms and four persons had extreme prostration.

The Porto Rican Commission is entirely in harmony with the exception taken by the writer to the opinion that large doses of thymol must necessarily be given. If a patient cannot stand a large dose, smaller doses will expel a few worms and thus enable him gradually to reach a condition in which the dose may be increased.

Beta-naphthol.—Possibly there is more diversity of opinion as to the use of this drug than in regard to any of the others used in hookworm disease. It is administered in the same routine as thymol. The doses vary, according to different authors, from $\frac{1}{2}$ to $1\frac{1}{2}$ the size of the thymol doses. Some authors use the prepurge and postpurge, others omit one or both. As compared with thymol, some authors consider it as less effective, others more effective, and some view its deleterious effects as less severe, others as more severe. It inhibits oviposition for four (Mhaskar) to ten days. Mhaskar (1924) administers (to Indian patients) beta-naphthol in a single dose (maximum for adult, 50 gr., mixed with 25 gr. of magnesium carbonate, taken in water); he reports 90 per cent. reduction of the infection by a single treatment and considers this drug safer than thymol.

Extract of Male Fern.—This drug has been used successfully in thousands of cases of hookworm disease. With other drugs producing less serious effects than male fern, the less severe drugs should, however, be shown preference. The dose is 4 to 8 cc. (about 1 to 2 fluidrams) followed by salts or calomel and salts.

Prevention.—Since the feces of hookworm patients represent the potential infection in concentrated form, it is clear that a proper disposal of the discharges is the greatest factor in preventing hookworm disease. Build proper privies and insist upon their being used; in mines, adopt the pail system. This one line of prevention, if carried out, is sufficient to blot hookworm disease out of existence so far as the Southern States are concerned, for fortunately we do not have to deal with specifically identical infections of the domesticated animals. In countries with anthropoid apes, complete eradication is complicated by the presence of any species of ape in which the hookworms of man might develop.

Numerous other preventive measures have been advanced, but while good in themselves, they fail to reach the source of the evil. The proposition to wear shoes and thus prevent ground-itch is of course a very good one, but financial considerations inhibit its universal adoption; if the infected feces are properly disposed of, ground-itch will practically disappear even if shoes are not worn. The proposition to drink boiled or filtered water is an excellent one, but of impracticable general application among the poor; but if the feces are disposed of, the danger of infecting the water is removed. To keep the hands clean is an excellent plan, but unfortunately one of limited application, especially in mines, brick-

PLATE V

The Kidney Worm (Dioctophyme renale) of Man, from a Specimen in a Dog. Natural size. Original.

yards, and among farmers. The great principle is to prevent the dirt from becoming "dirty;" clean dirt is not dangerous.

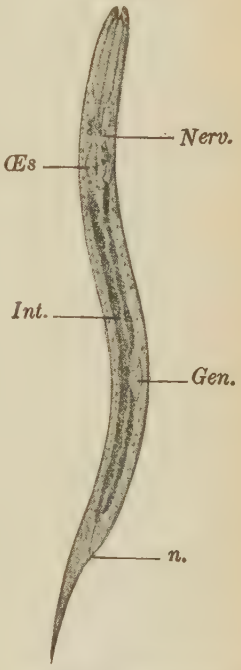
In countries (Brazil, Philippines, Ceylon, etc.) in which *A. braziliense* or *A. ceylanicum* occurs, the problem is complicated by the fact that these parasites occur in dogs and cats.

Strongyloidosis.[1]—Infection with *Strongyloides stercoralis.*—**Geographical Distribution.**—The distribution of this infection is much more general than was formerly supposed; it seems to be especially a tropical and subtropical species, but as such probably encircles the earth. American cases have been found, locally, as far north as Baltimore and imported or migratory cases even farther north. European cases have been found as far north as Belgium, England, Germany, and Holland, and the infection is also reported for Siberia. It is known also for Asia, Australia, Africa, Central and South America, and various tropical islands.

Zoölogical Distribution.—Strong (1901) reports this parasite for monkeys as well as man, and he was able to transmit the disease to monkeys by feeding infected human excreta to them. A species (*S. canis*) is reported for dogs which may be distinct from (or identical with?) *S. stercoralis* of man.

The Parasite.—I. (*a*) The *parasitic* (intestinal) *adults* are parthenogenetic (or hermaphroditic?) females, measuring 2.2 to 3 mm. long by 34 to 70 μ broad, with an œsophagus about one-fourth as long as the body; a double uterus is present, each horn containing 3 to 6 segmenting eggs (50 to 59 by 30 to 34 μ) which escape through the vulva, situated in the posterior third of the body. These eggs are deposited in the intestinal lumen of the host or in galleries in the intestinal mucosa made by the females, and develop into — (*b*) *Rhabditiform embryos*, 200 to 300 μ long by 12 to 16 μ broad, which may grow to 450 to 600 μ long by 16 to 27 μ in diameter by the time they are discharged with the feces. The buccal cavity is short, relatively broad, and without thickened chitinous lining. These embryos develop within two to three days into —II. (*c*) *Free-living dioecious adults.* The *males* measure 0.7 mm. long; the tail is curved ventrad to form a hook; spicules curved, 38 μ long. The *females* measure 1 mm. long; vulva slightly postequatorial. Each female develops 30 to 40 eggs which may or may not segment in the uterus; these eggs develop the—(*d*) *Free-living rhabditiform embryos*, which measure 220 μ long; when they attain 550 μ in length, they moult and at the

Fig. 90



Larva of *Strongyloides stercoralis* as found in fresh feces; *Nerv.*, nervous systems; *Œs.*, œsophagus; *Int.*, intestines; *Gen.*, genital primordium; *An.*, anus. × 228. (Looss.)

[1] Synonyms.—Anguilluliasis, Rhabdonemiasis. See especially Strong (1901) and Thayer (1901).

same time change to—(*e*) *Filariform larvæ*, possessing an elongate cylindrical œsophagus about one-half as long as the body. This is the infecting stage, which enters man by the mouth or through the skin, reaches the duodenum and upper part of the jejunum either *via* the lungs or more directly, and in two to fifteen days develops directly to (*a*) the parthenogenetic females.

The complete life cycle (*a-b-c-d-e-a*) is thus an alternation of a diœcious with a parthenogenetic generation (alloiogenesis) and is the cycle reported more commonly in tropical and subtropical cases. In other cases, notably in the temperate zone, an abridged cycle consisting of *a-b-e-a* may occur; thus there is a tendency to a more completely parasitic life by the omission of the free-living diœcious generation. There must be various factors, influencing the changes in the life cycle, that are not clearly understood.

Source of Infection.—Infection takes place in either of two ways, passively by means of contaminated food or drinking water, or actively through the skin.

Frequency.—Extensive statistics of a satisfactory nature are not accessible, especially since this worm has so frequently been confused with other species. In general, the infection increases in frequency from cooler to warmer climates. In Washington, D. C., several cases have been known (probably none contracted within the city); the microscopic examinations in the Rockefeller hookworm campaign clearly demonstrate that the infection is much more common in this country than is generally supposed. Powell found it in 75 per cent. of the cases of anemia in India (Manson). Statistics for various countries vary from 0.1 to 35 per cent. infection among the persons (often special cases) examined.

Duration.—The longevity of the individual worm is not established. Cases of infection are known of several (up to thirteen) years' standing, due possibly to reinfection. Ward (1903) suggests that the very heavy infections occasionally reported possibly point to an endless chain multiplication by means of the abbreviated cycle (*a-b-e-a*) in the intestine —as might perhaps occur in cases of constipation.

Symptoms and Pathology.—The literature contains extreme statements that the parasite is utterly harmless and that it is exceedingly injurious. A number of authors see in this parasite a worm which may indeed in some cases be apparently harmless, but which, in large numbers, may cause "clinically, an intermittent diarrhœa with intestinal disturbances, and pathologically, a catarrh of the small intestine" (Strong). At the Marine Hospital, Wilmington, N. C., we were thoroughly persuaded that the parasite may be of serious import, probably more so in white patients that in negroes. The percutaneous infection results in pruritus, local urticaria, and a papular eruption and œdema which may last more than a month. The syndrome of "Gale des mineurs" (miners' itch) can be caused by this parasite as well as by hookworms. Barlow (1915) recognizes four stages in the disease: (1) Cutaneous, (2) latent, (3), diarrhœa, and (4) neurasthenic.

Clinical Diagnosis.—The only possible method is by microscopic examination of the feces: (1) Examine *fresh* feces for the rhabditiform embryo (Stage *b*) or (2) make cultures of equal parts of feces and of animal

charcoal to raise the free adult generation (Stage *c*). In violent purging, eggs, strung together end on end and surrounded by a delicate tube, may appear in the stools. In general, *fresh* feces show hookworms in the egg stage, but *Strongyloides* in the embryo stage; in feces a day or more old, either (or both) hookworm embryos or (and) *Strongyloides* embryos may be present; the pharynx of the hookworm embryo is as long as the diameter of the body at the base of the pharynx; that of the *Strongyloides* embryo is one-half as long as the diameter of the body at the base of the pharynx. In feces which are not fresh, confusion may occur because of contamination by free-living nematodes (such as *Diplogaster*).

Treatment.—Repeated doses of thymol as used in hookworm infection are usually advised for strongyloidosis, also but owing to the fact that parasites may burrow, treatment is reported as unsatisfactory. In the experience of the writer, thymol treatment is much less satisfactory than is usually supposed; at the Marine Hospital we have seemingly had sufficiently encouraging results with flowers of sulphur to warrant the suggestion that it be given a fair trial. The drug (flowers of sulphur) is given in 5 to 15 gr. doses (0.3 to 1 gm.) three times a day, in capsules with equal parts of sugar of milk. Oil of chenopodium is reported as giving satisfactory results.

Prevention.—Same as that for hookworms, see p. 574.

Ascariasis—Eelworm Infection.—Geographical Distribution.—Cosmopolitan, more in rural districts than in cities.

Zoölogical Distribution.—A number of authors maintain that the common ascarid of man occurs in certain domesticated animals, such as the pig, horse, cattle, etc. This view is not in harmony with the present zoölogical classification which recognizes these infections as generically identical but specifically distinct. Experimental evidence is, in fact, accumulating to the effect that the ascarid of swine will not mature in man.

Fig. 91

Egg of the common ascaris (*Ascaris lumbricoides*) of man as found in feces. Seen with superficial focus. Greatly enlarged. (Stiles.)

The Parasites. — *Ascaris lumbricoides* Linnaeus, 1758, is, in general terms, about as large as an ordinary lead-pencil but tapering toward both ends; the male measures 15 to 17, even 25 cm, in length by about 3 mm. in diameter; the female is somewhat larger, 20 to 40 cm. in length by 5 mm. in diameter, and is oviparous. The worms are grayish to reddish-yellow in color; the anterior end is provided with three lips. The egg is 50 to 87.5 by 36 to 57.5 μ, unsegmented when oviposited, and provided with a thick mammillate covering, frequently tinged yellow when found in the feces. The parasites live in the small intestine. Development is direct, without intermediate host.

When embryonated eggs of *Ascaria suum* (Goeze, 1782) are swallowed by man, the larvæ may reach the lungs and produce an *Ascaris* pneumonia but they do not reach maturity in the intestine. The present evidence is that this worm is at least physiologically distinct from *A. lumbricoides*.

When embryonated eggs of *A. vitulorum* (Goeze, 1782 *a*) were swallowed

by Martin, the worms attained 8 mm. in length in twenty-five days, but evidence is lacking to prove that they mature in man.

(?*Ascaris*) *texana* Smith and Goeth, 1904, has been described as a new ascarid for man in Texas; it measures 58 to 60 mm. in length and is said to possess intermediate lips; uterine eggs segmented, 60 by 40 μ. Through the kindness of the describer, Allen J. Smith, the writer was enabled to examine the original specimens; the structures described as intermediate lips do not correspond to the intermediate lips so far as he is familiar with them in other species of *Ascaris* but as the material was poor the writer refrains from expressing any definite opinion regarding this species, which is still *sub judice.*

At least three species (*canis, cati, minor*) of arrow-headed ascarids have been reported for man.

Ascaris (*i. e., Toxocara*) *canis* (Werner, 1782) of dogs has been reported for man, but its occurrence in man is *sub judice.*

Toxocara cati (Schrank, 1788) (syn. *Asc.* seu *Belascaris mystax*) of cats has been reported in 9 cases in man. The male is 40 to 60 mm., female 120 to 180 mm. long; eggs 65 to 80 μ; shell areolated. *Toxascaris limbata* (Rail and Henry, 1911), of dogs, has been reported for man in Egypt.

Several additional species of *Ascaris,* sensu lato, have been reported for man under the names *A. capsularia, A. clavata* (in a tooth), *A. lumbricoides rostratus, A. triquetra, A. ventriculi,* and *A.* species Welmann, 1905 (for Angola), but they are not recognized to-day as established parasites of man.

Source of Infection.—The egg escapes in the feces and slowly (in ten days to several months, according to conditions) develops an embryo; no intermediate host is required at least for *Ascaria lumbricoides* and *Toxocara canis;* but when the developed eggs are swallowed, either in contaminated food or water, or from hands soiled with dirt containing the eggs, they pass to the small intestine where they hatch; the embryo migrates *via* the portal vein to the liver, where it may remain for several days; passing with the blood to the right side of the heart, then to the lungs, it filters out into the air passages, passes up the bronchi and trachea, down the œsophagus, through the stomach to the small intestine; during this migration, which lasts about ten days, the worm increases to about 1.5 mm. in length; it becomes mature in about ten weeks. Percutaneous infection also is reported in experimental animals.

Frequency.—The ascarid is one of the most common parasites of man; it may occur at any age, from about eight months to eighty-five years, but is usually more frequent in childhood (from five to ten years) and youth than in adult age, and more common in women than in men. Autopsy statistics for Germany (Heller and Müller) give the following combined results: Males, 220 cases in 2275 autopsies, or 9.67 per cent.; females, 194 cases in 1446 autopsies, or 13.41 per cent.; children, 101 cases in 584 autopsies, or 17.29 per cent. It was present in 0.49 per cent. of 3457 persons of one group (Washington, D. C.) and 1.1 per cent. of 8029 of another group (U. S. A.) examined under direction of the writer. In Porto Rico, Guam, and the Philippines it is excessively common.

Usually only from 2 to 6 individuals are present in one patient, but infections with 30, 40, 100, 140, and 300 to 600 worms are recorded, while Fauconneau-Dufresne (1880 *a*) reports the case of a boy, aged twelve years, who passed (chiefly by vomiting) more than 5000 worms within less than three years, 600 being passed in one day.

In general terms *Ascaria lumbricoides* is more common in warmer than in temperate and colder climates, and more common in the rural districts than in the cities. Authors attribute its greater frequency in rural patients to the use of unfiltered water, but other factors, such as soiled fruit and soiled vegetables seem to be of more importance; in cities with a sewage system the infectious material is carried away, while in country districts the surface privy affords greater possibilities for the spread of infection.

Duration.—Definite details as to the longevity of the individual parasites are lacking.

Symptoms.—Experiments to demonstrate the life cycle of the parasite have placed the early stage of the infection on a more important basis than was formerly appreciated, for they have shown the existence of an "*Ascaris* pneumonia," which will naturally vary in proportion to the number of eggs swallowed and the strength of the patient. Two experimental cases are especially instructive, one by Koino (upon himself with *A. lumbricoides*), the other upon his brother (with *A. suum* of hogs, this latter case being suggestive in connection with pneumonia especially in rural districts); on the sixth to the ninth day after infection, "*Ascaris* pneumonia" developed, with initial chills, followed by headache, fever, difficulty in respiration, cough, profuse sputum, hemoptysis, pains in the chest, bronchitis, muscular pains and olfactory hypersensibility; recovery occurred in three to eight days.

Very frequently symptoms are lacking. In other cases they are more or less indefinite, practically all the symptoms reported for tæniasis and oxyuriasis being recorded for ascariasis. Among those recorded may be mentioned: irritation of the skin, urticaria, pallid appearance, alternate pallor and redness of the face, jaundice, dark rings around the eyes, unequal or dilated pupils, flashes before the eyes, mydriasis, amblyopia, amaurosis, strabismus, disturbances in sight and hearing, inflammation of the eye, itching of and picking at the nose, grinding of the teeth, bad taste and offensive breath, dry cough, hiccough, aphonia, anorexia, irregular or capricious appetite, dirt-eating, eructations, sensibility of stomach on pressure, nausea, vomiting, gastrorrhagia, vague abdominal pain, borborygmi, colicy pains, cramps, irregular bowels, diarrhœa, constipation, intestinal obstruction, meteorism, itching at the anus, muscular pains, progressive emaciation, headache, vertigo, fretfulness, fainting spells, chorea, convulsions, epilepsy, catalepsy, ecstasy, hysterical conditions, eclampsia, neuralgia, paralysis, psychoses, tetanoid states, pseudomeningitis, palpitation and irregular action of the heart, syncope, etc.

While many physicians recognize elements of danger in an infection with ascaris, others sometimes view these worms with little more than a passing curiosity. Hundreds of cases of ascariasis, recognized or unrecognized, may pass through a physician's hands without any fatal results.

Still, the occasional danger is deserving of attention and (especially in rural practice) this infection is to be considered in differential diagnosis of pneumonia, appendicitis, and hookworm disease. If a light infection is present, the chances are very great that nothing serious will result; but unfortunately the worms have a habit of wandering, especially in febrile conditions, and medical literature shows that these wanderings, even in light infections, present a dangerous aspect of the disease. The escape of erratic ascarids by the mouth or nose is not very rare. If during this wandering the worm comes into contact with an ulcer, perforation into the abdominal cavity or the lungs may result; or the worm may enter the Eustachian tube and escape by the external ear; in some cases it enters the lacrimal duct; or it may turn at the larynx and pass a greater or less distance down the trachea and bronchi, in some cases causing suffocation, in others abscess or gangrene of the lungs; about 40 cases are recorded in which ascards have entered the air passages. About 100 cases are recorded in which the worms have wandered into the bile ducts, 9 cases into the pancreatic duct, and some 20 cases into the urinary passages. In some cases the worms pass into the abdominal cavity, either piercing the intestinal wall or working their way through an ulcer. Blanchard compiled 81 cases in which ascarids escaped through the body wall; 29 cases through the umbilicus, 30 through the groin, 10 at unstated points of the abdomen, 2 by the hypochondrium, 2 by the lumbar region, 2 by an inguinal abscess, 1 each by the sacral, pubic, and perineal region, and abscess of the thigh, inferior portion of thorax and linea alba. Davaine points out that, corresponding to hernia, ascarids escape by the umbilicus more frequently in children than in adults, and by the groin more frequently in adults than in children.

In view of the foregoing brief account of erratic ascarids, in not a few cases fatal, it is at least worth while, from a prophylactic standpoint, to treat all cases which are found, even independently of the question as to whether any moderate or serious local or perhaps reflex symptoms are traced to the presence of the worms in the patient under consideration. That heavy ascarid infections, such as are found in unhygienic tropical countries, may be of considerable clinical importance is evident. Such cases may be easily subject to an erroneous diagnosis of hookworm disease, pneumonia, typhoid fever or appendicitis, especially in children.

Ascaris sensitization is an occupational disease among scientists who study these worms and is to be considered as a possibility among persons employed in slaughter houses, especially among the "gut-cleaners." The symptoms immediately suggest a similarity to those seen in hay fever, asthma and other conditions grouped under the heading of foreign protein sensitization. Among the symptoms are irritation of the mucous membrane of the eyes, nose, and throat, lacrimation and œdema of the eyes, facial œdema, sneezing, coughing, swelling of the nasal mucosa, increased nasal and bronchial secretions, painful deglutition, urticaria, asthma, headache, fever, pruritus, tingling and burning sensations, swelling of the fingers, lassitude and weakness, sometimes amounting to prostration. In some cases asthmatic attacks have persisted for weeks after exposure, but it is not certain in these cases that the possibility of

subsequent exposures was entirely excluded. The severity of the symptoms may increase with repeated exposures. Sensitive individuals exhibit a positive skin reaction to a substance contained in aqueous extracts of the ascarids of man and pigs, similar to the reaction exhibited in cutaneous tests for so-called foreign protein sensitization (Ransom, *et al.*, 1924).

Diagnosis.—It is possible to make a diagnosis independently of symptoms, either by a microscopic examination of the feces to find the characteristic eggs, or by recognition of worms passed.

Treatment.—Santonin is the classical drug for ascariasis. It is given in powder, coarse crystals, or troches; the coarse crystals are safer than the powder, as they are less readily dissolved and thus less likely to be absorbed from the stomach; santoninates and combinations of santonin with alkali carbonates or hydroxides are to be avoided. Accepted doses are: 0.01 gm. per day ($\frac{1}{6}$ gr.) for each year of the child's age, 0.06 to 0.3 gm. (1 to 5 gr.) for an adult; deaths are reported from doses of 2 gr. (a feeble child, aged five years) and 6 gr. (child of six or seven years old); very serious symptoms are reported in a child, aged four years, to whom 4 gr. were administered. The drug is best given with an equal or greater amount of calomel, every morning two or three days in succession; then repeat the medication every three or four days as long as eggs are found in the feces or until further worms are not expelled. In treating children it is well to forewarn the mothers of the possible effects of santonin upon the patient.

Among other drugs used for the expulsion of ascarids may be mentioned: Oil of chenopodium, 0.13 to 0.6 cc. (2 to 10 minims) on a lump of sugar or in emulsion, before meals (see also p. 572), followed by a purge (calomel). Thymol is sometimes recommended, but at the Marine Hospital in Wilmington, N. C., it has not given satisfactory results.

Serious intestinal obstruction by ascarids should be treated as obstruction from any other cause.

Oxyuriasis.—Pinworm Infection.—Geographical Distribution.—Cosmopolitan, independent of climate.

Zoölogical Distribution.—The pinworm of man is not known to occur in any other animal; closely allied infections are, however, known for a number of mammals.

The Parasite.—*Enterobius* (formerly *Oxyuris*) *vermicularis*[1] (Linnaeus, 1758), known as the pinworm, seatworm, also mawworm, is a small, white, roundworm measuring 2 to 5 mm. (male) to 12 mm. (female) in length, 0.16 to 0.6 mm. in diameter; the male has but one spicule; the female is provided with a relatively long, sharply pointed tail; the vulva is preëquatorial; two uteri are present filled with numerous embryonated eggs 50 to 60 by 16 to 32 μ, with relatively thin shell, and with dorsal surface much more convex than the ventral. The young parasites live in the small intestine, where the worms copulate. The fertilized females wander to the cecum, and later when gravid to the colon. The life cycle lasts about two weeks, It has been maintained that the normal loca-

[1] Synonyms.—*Oxyuris vermicularis; Oxyurias vermicularis; Trichina cystica* Salisbury, 1858; *Filaria cystica* (Salisbury) Railliet, 1893, in part only (not *F. cystica* Rudolphi, 1819).

tion for pinworms is the vermiform appendix; it cannot be doubted that pinworms do enter the appendix as Heller, for instance, reported 36 males in 1 case: 19 males and 19 females in another; 30 males and 9 females in another; 46 males and 27 females in another; and pinworms have been incriminated as possible cause in certain cases of appendicitis; Railliet (1911) reported it in 59 cases (=48.7 per cent.) of 119 inflamed appendices; but it hardly seems proved that the appendix is the normal habitat for these parasites. The statement occasionally found that the embryo escapes from eggs oviposited in the rectum and develops there into an adult is possibly traceable to Vix (1860); but this view cannot be accepted.

Fig. 92

Embryo of the common pinworm (*Enterobius vermicularis*) of man, in the egg-shell, as found in fresh feces. (Leuckart.)

Oxyuris incognita Kofoid and White, 1919, was described from eggs (60 to 133 by 33 to 43 μ) found in the feces; the adult has never been recovered from man. Sandground, noticing the resemblance these ova bear to *Heterodera* (seu *Caconema*) *radicicola*, ate plant roots containing this nematode and removed from his feces ova which could not be distinguished from those of *O. incognita*.

Syphacia (formerly *Oxyuris*) *obvelata* (Rudolphi, 1802), a pinworm of rats, has been reported once for man in the Philippines.

Source of Infection.—Pinworms have a pronounced tendency to wander out of the anus, and when the female is crushed by scratching with the fingers, to relieve the irritation, a person infects his fingers, especially under the finger nails, with the embryonated eggs; from the fingers to the mouth or nose is but a short distance, and autoinfection thus occurs. Or the embryos in the bedclothes may easily soil the hands of a bed-fellow, a companion, or a nurse, and be transmitted to a second person. Or the eggs (free in the feces or in the body of the discharged female worms) may be transmitted by means of contaminated food. No intermediate host is necessary. Theoretically it seems possible that flies may occasionally play a role in the mechanical dissemination of the eggs. Food, contaminated from excreta or from the hands of cooks, etc., can carry the infection; but drinking water plays little if any role as a medium of transport, since the embryo is very sensitive to its effects.

Frequency.—This parasite is one of the most common of the intestinal worms. It is more frequent in children (from three to ten years) and women, but has been observed in babes of five weeks up to men of eighty years. It was found in 1.3 per cent. of 3457 persons examined under the writer's direction at the Hygienic Laboratory at Washington. Heller reports it in the proportion of 33.8 per cent. for children, 21.1 per cent. for women, and 18.8 per cent. for men, in 611 autopsies at Keil, Germany. Infections are reported as more common in the spring than at other seasons of the year. The number of specimens of pinworms in one person varies from a few to such heavy infections that the mucosa of the large intestine may be covered with them.

Duration.—The longevity of the individual worms is not established. Cases of infection of ten to fifteen years and even much longer are recorded but these are perhaps due to repeated autoinfection.

Symptoms.—Doubtless many cases of light infection pass unnoticed, and in case the person is of clean personal habits, the infection dies out, In heavy infections there may be marked irritation of the intestinal mucosa, resulting in a catarrhal condition and diarrhœa; there may be foul breath, nausea, vomiting, abdominal pain and tenesmus; further, one may find headache, restlessness, sleeplessness, itching at the nose, vertigo, unequal pupils, chorea, and even dysmenorrhœa, masturbation and convulsions. One of the most constant symptoms is intense itching and burning at the anus, due to the wandering of the female, especially shortly after the patient retires; the anus appears red, irritated, sometimes bloody; reaching the perineum the worms may pass to the vagina if the skin is moist, and may here cause hyperemia, increased secretion of mucus, and sometimes hyperesthesia and leucorrhœa; sexual excitement may result; cases are recorded in which the worms have ascended into the uterus and produced metritis. Wandering pinworms have been found in the vagina, uterus, and even in the abdominal cavity.

Pinworms are to considered as occasional factors in appendicitis. Of 800 autopsies in Paris, pinworms were observed in the appendix in 3.5 to 4 per cent.; of 234 cases of operated appendicitis, collated from various sources, pinworms were found in the appendix in 23 per cent.

Diagnosis.—While symptoms may indicate pinworm infection, a positive diagnosis may be made in several different ways: the adult worms may be found in the stools, occasionally in considerable numbers; or they may be found in the crotch, especially if the child is examined during the restless period after retiring; a microscopic examination of scrapings around the anus, or the cleanings from the finger nails may reveal the characteristic eggs; finally, the eggs may be discovered by a microscopic examination of the feces. Opinions are divided regarding the value of the last; some authors consider that the eggs are not found free in the stools, while others state that they are common. The writer's experience is that the eggs may be found in fecal examinations; a negative examination is not of much value.

Treatment.—This should take into consideration two distinct points: namely, not only the removal of the gravid female pinworms from the rectum, but also the removal of the younger worms from the small intestine. A failure to consider this latter point doubtless explains not a few cases of treatment which have not met with success. For removing the younger pinworms from the small intestine, several drugs may be used, as santonin and calomel (of each 0.05 to 0.1 gr.—$\frac{3}{4}$ to $1\frac{1}{2}$ gr.) given several days in succession (see also p. 581), or large potions of an infusion of gentian or active saline cathartics repeated several days in succession, or thymol or oil of chenopodium. Ungar gives immediately after a laxative, four doses per day of naphthalin (0.1 to 0.4 gm.—1.5 to 6 gr.) according to age, for two or three days in succession between meals.

To expel the gravid females from the rectum, rectal injections are used. An infusion of quassia seems to be one of the most popular remedies. Other commonly used enemata are: lime-water, salt and water, iced water, salt and milk (highly spoken of), cold water, aloes, diluted vinegar (which should be sterilized before using, otherwise the patient may become

infected with vinegar-eels), perchloride of iron, glycerin, benzine (20 drops to a pint of warm water), finely chopped garlic with water (which has stood for twelve hours and is then strained through linen).

The injections are given with the buttocks elevated, or in the knee-chest position, at first every evening, then every two or three or four evenings, until all evidence of worms has disappeared. If too large an injection is given to be retained this washes out a number of worms; but it should be followed by a small injection, 2 to 4 ounces, or an amount which can be conveniently held.

Ointments of various kinds may be applied to the anus and perineum to relieve the itching.

Physaloptera caucasica (Linstow, 1902), has been reported but once for the intestine, in Caucasus. Length 14 (male) to 27 (female) mm., breadth 0.71 to 1.14 mm. Eggs 57 by 39 μ.

Physaloptera mordens (Leiper, 1908), is reported from the œsophagus, stomach, small intestine, and liver of natives in tropical Africa, and it also occurs in *Simia*. The male worms measure 30 to 50 mm. long, the females 40 to 55 mm. long by 2 to 3 mm. broad; the males have unequal spicules, 4.6 and 0.6 mm. long and a pair of caudo-lateral cuticular expansions provided with paired pedunculated papillæ in addition to the more median-situated sessile papillæ on the body; eggs 43 by 35 μ. These worms may be easily mistaken for young specimens of *Ascaris*, but they have two lips instead of three.

Œsophagostomum.—This genus contains worms that might at first sight be mistaken for hookworms, but the head is straight; the mouth is provided with a chitinous ring, followed by a cuticular swelling interrupted ventrally by a transverse constriction. Three different worms of this genus have been described as parasites of man, namely:

Œsophagostomum (*Conoweberia*) *brumpti* Railliet and Henry, 1905, in tumors of the colon, in a Pouma negro on the Omo River, Africa. Females, 8.5 to 10.2 mm. long by 0.295 to 0.325 mm. in diameter; vulva 0.35 to 0.495 mm. from tip of tail and cephalad of anus. The same parasite is reported for monkeys (*Cercopithecus callitrichus, Cynocephalus*).

Œsophagostomum apiostomum (Willach, 1891), larva in hemorrhagic cysts in wall, adult in lumen of colon and cecum, of a negro in Nigeria. It was first reported from a monkey (*Macacus cynomolgus*). The male measures 8 mm., the female 10 mm., long. According to Railliet and Henry, the parasite in man (*Œsophagost.* species Brumpt, 1922) is not a true *Œ. apiosotomum.*

Œsophagostomum stephanostomum thomasi Railliet and Henry, 1909, larva in nodosities of intestinal wall, in Amazon, Brazil.

Ternidens deminutus (Railliet and Henry, 1905) was described from specimens which were probably the original worms in Monestier's (1867*a*) paper on chloro-anemia in a Makouan negro at Mayotte; Monestier thought they were hookworms. The head is nearly straight, the mouth dorso-terminal and surrounded with a fringed collar of 22 rounded lamellæ; male 9.5 mm. long, spicules 0.9 mm. long; female 12 to 16 mm. long, vulva preanal, 0.68, mm. from tip of tail. Turner (1910) reports this species in natives from Nyassal and it is also reported for *Macacus sinicus* of India and *Macacus cynomolgus* of Saigon.

Strongylus gibsoni (Stephens, 1909), recorded in the feces of a Chinese at Hongkong is a *Mecistocirrus*, variously interpreted as *M. fordi* (of buffalo) and *M. digitatus* of cattle and swine.

Haemonchus contortus (Rudolphi, 1803) is an exceedingly common parasite in the stomach of cattle, goats, and sheep. It is reported once (Magalhães, 1908) in a man, in Santa Vitoria, Argentine, who exhibited symptoms of uncinariasis.

Trichostrongylus[1] (Looss, 1905.)—Four small intestinal species *instabilis* (Rail., 1893), *Tr. probolurus* (Rail., 1896), and *Tr. vitrinus* Looss, 1905, in Egypt; *Tr. orientalis* Jimbo, 1914, in Korea and Japan) have been reported for man. They do not seem to be important parasites, and their normal habitat seems to be other animals (sheep, antelope, dromedary, baboon) rather than man. They measure 4 to 6 or 7 mm. in length. Their eggs may be mistaken for hookworm eggs, but are in general somewhat larger, 73 to 90 μ long and are oviposited in the 8 to 32 cell stage.

Anguillulina putrefaciens (Kühn, 1897).—Small nematodes of various sorts gain access to the stomach by being swallowed accidentally with food (vegetables, vinegar, water, etc.), and the worms or their eggs are likely to appear either in the vomit or in the feces. As an example of this sort reference may be made to *Anguillulina putrefaciens* reported by Botkin (1883) as *Trichina contorta*, in the vomit. The worms gained access to the stomach in onions and caused vomiting.

Rhabditis hominis (Kobayashi, 1915), is a small nematode, 0.9 to 2 mm. long, reported in the intestine of children in Japan and the United States. In general it takes an expert to classify the small worms of the group to which this species is assigned; as they are of no known medical importance, except in differential diagnosis, it is sufficient to determine them as *Rhabditis* without attempting to recognize the species. Other forms reported for man are *R. foecalis* Watanabe, 1922, and *R.* species Trese, 1907 (in stomach).

Trichocephaliasis.—Whipworm Infection.—Geographical Distribution.—Probably cosmopolitan.

Zoölogical Distribution.—The whipworm of man is said to occur also in various apes and lemurs; generically identical but specifically distinct infections are more or less common in dogs, cattle, sheep, and a number of other animals.

The Parasite.—*Trichuris trichiura*[2] (Linnaeus, 1761), the whipworm, has the general form of a whip, the posterior swollen body representing the handle, and the lash representing the slender filiform anterior portion. The male measures 30 to 45 mm., the female 35 to 50 mm. in length. The parasites inhabit the cecum, but are occasionally found in the vermiform appendix and in the colon, rarely in the small intestine. They produce numerous characteristic eggs, 50 to 54 by 21 to 23 μ, of a yellowish to

[1] The synonymy is slightly confused: *Strongylus instabilis* Railliet, 1893 *a; S. subtilis* Looss, 1895; *Trichostrongylus subtilis; Tr. instabilis.* These are synonyms of *Tr. colubriformis* (Giles, 1892), fide Lane and Brumpt.

[2] Synonyms.—*Ascaris trichiura; Trichocephalus hominis; Trichoc. dispar; Trichoc. trichiurus* of various authors.

dark brown color, with unsegmented protoplasm and with a peculiar light spot at each pole resembling apertures.

Source of Infection.—The eggs develop slowly after being discharged in the feces, and with the contained embryo are swallowed in drinking-water or contaminated food. An intermediate host is not necessary.

Frequency.—This is one of the most common parasites of man, varying in frequency from less than 1 per cent. up to 100 per cent. of persons examined in different parts of the world. In general terms it is more common in warmer than in colder climates. In Washington, according to examinations made under the writer's direction, it is twice as common in negro as in white children; it was present in 7.69 per cent. of one group of 3457 persons examined by the Zoölogical Division of the Public Health Service; but in only 2.1 per cent. of 8029 persons (from various States; chiefly ex-soldiers) of another group (1920–1921); it may vary greatly in frequency in different wards of the same asylum; in the United States Government Hospital for the Insane 10.8 per cent. of 500 white male patients were infected, the highest percentage being 38.98 in soldiers returned from the Philippines. It is most frequent in children from three to ten years of age.

Fig. 93

Egg of whipworm. × 400. (Looss.)

Duration.—The length of life of the individual parasite is not established.

Symptomatology and Pathology.—The opinions expressed regarding this worm have been frequently characterized by extreme statements, varying from the view that it is of no medical importance whatever, to the view that it is the cause of very serious disease. That, in the vast majority of cases, it is of scarcely any appreciable importance, and that its presence cannot be recognized symptomatically may be conservatively admitted. But that severe infections do not produce injury is not in accord with probability or recorded observations. According to some observers, the worm simply lies loose on the intestinal mucosa; but other competent observers report finding its head burrowed in the epithelium. Askanazy reports hemoglobin in the worm's intestine, and several cases of severe anemia have been recorded, which were apparently justly attributed to heavy infections with whipworms. Andrikidis (1906) refers to digestive and nervous symptoms and anemia, and says there may be a picture of recurrent appendicitis. Guiart, of Paris, suggested that the wounds made by whipworms form the point of entrance for the typhoid bacillus. Examinations made at Washington do not bear out this hypothesis for this locality.

Clinical Diagnosis.—The only method is by microscopic examination of the feces for the characteristic eggs.

Treatment.—Medical writers agree that treatment is unsatisfactory. Thymol is recommended but in laboratory experiments on the dog, Pfender and the writer found it worthless in whipworm infections. In the literature on hookworm disease, frequent mention is found of the expulsion of whipworms by male fern administered in treating uncinariasis.

Hemmeter (1902) advises irrigation of the colon with benzine (1 dram of benzine to 1 quart of warm water) and at the same time internal administration of benzine. Doliarina, in massive doses, is recommended in South America with reported success.

Prevention.—A proper disposal of the feces is of first importance. Personal cleanliness, the use of proper drinking-water, and the disuse of surface-water for drinking purposes contribute to prevention.

Infection with Mermithidæ.—These infections are of little significance. At least one recorded as filarial in nature probably belongs here.

(?Filaria) hominis oris Leidy, 1850, has been reported once "from the mouth of a child;" it measured 5 inches, 7 lines long, by $\frac{1}{6}\frac{1}{4}$ of an inch in diameter. Nothing is known of its anatomy. It seems very possible that this may have been an *Agamomermis* obtained in eating an apple.

Gongylonema.—The future role of *Gongylonema* in human medicine cannot be definitely foreseen but its potentialities are suggestive. Species of this genus are rather common in the wall of the stomach and œsophagus of rats, mice, cattle, sheep, goats, etc. Insects (cockroaches, croton bugs, etc.) act as intermediate hosts. *G. neoplasticum* is commonly associated with cancer of the stomach in rats, but *G. scutatum*, which is very common in the œsophagus of cattle, and other species, in various animals, are not known to be concurrent with cancer. Several cases of the presence of *Gongylonema* causing considerable irritation in the buccal membrane of man have been reported for the United States and Italy and although none of the patients is known to have had cancer, the question has naturally arisen whether this genus may be one of the exciting causes of cancer in man. In view of the facts that a widely distributed household insect (cockroach) can act as intermediate host for species of this genus, that this insect can be so easily ingested accidentally with food, and that the normal organ-habitat of the worms corresponds to a frequent organ-location of cancer, it will be wise to hold in mind the possibility suggested; but the present author is not yet prepared to attach to it the importance recently suggested by Sambon.

The specimens recovered from patients have not been sufficiently numerous or mature to permit of definite specific determination, nor is it yet possible critically to define the relations which may exist between these worms and the congeneric parasites of other animals. As found in man, the worms are thread-like, much like *Filaria*, about 30 to 42 mm. long; the cuticle of the œsophageal zone is provided with peculiar, more or less symmetrically placed shield-like elevations (quite distinct from the bosses of *Loa*), and the vulva is in the caudal quarter, somewhat preanal. The worms crawl around in the mucosa, from which they can be easily extracted.

The parasites from man have been assigned to three species, *G. hominis* Stiles, 1921 (tentatively determined as *G. pulchrum* Molin, 1857, by Ward, 1916, on the premise that this may be the same parasite which occurs in pigs) in the United States, and *G. labialis* (Pane, 1864) and *G. subtile* Ales., 1914, in Italy; the suggestion by Baylis (1925) that the worms in man are specifically identical with the form found in gastric cancer of rats is *sub judice*.

Infection with Gordiacea.[1]—A number of different horse-hair worms are reported as accidental intestinal parasites in the intestine of man. They are, however, rare and their effect temporary. At least 8 cases are known for North America; in 6 of these the parasite was *Paragordius varius*.

Infection with Thorn-headed Worms (Acanthocephala).—The thorn-headed worms differ from the nematodes in two chief characters: namely, in the absence of an intestine and in the presence of a retractile rostellum armed with hooks. An intermediate host (insects of various kinds) is required for their life-cycle. This group of parasites is of very little known importance in human medicine, but of greater importance in comparative medicine. Three species have been recorded as intestinal parasites of man, namely:

Macracanthorhynchus hirudinaceus[2] 10 to 50 cm. long; eggs 80 by 100μ long, with three shells; very common in hogs; May-beetles and June-bugs are the intermediate host; alleged to occur in man in South Russia.

Moniliformis moniliformis[3] (Bremser, 1819), 4 to 8 cm. long; eggs 85 by 45 μ; occurs in rats and certain other rodents; it is also reported for the dog; a beetle (*Blaps mucronata*) is the intermediate host; raised in man experimentally by Grassi and Callandrucio (1888 *c*). According to Magalhães, the large roach (*Periplanata americana*) may also serve as intermediate host and Seurat (1912) states that in Algiers the common cockroach plays this role.

Echinorhynchus hominis Leuckart, 1876, a doubtful species, 5.6 mm. long, reported but once.

In infections with thorn-headed worms, the diagnosis should be made by microscopic examination of the feces to find the eggs. Treatment is the same as for *Ascaris*.

INTESTINAL AND MUSCULAR ROUNDWORMS

Trinchinosis or Trichiniasis.—Infection with *Trichinella spiralis*.

Geographical Distribution.—Trichinæ are practically cosmopolitan, because of the wantering of rats; but trichinosis as a recognizable disease in man is practically limited to persons who indulge in the mis-custom ("Unsitte") of eating raw or rare pork.

Zoölogical Distribution.—From a practical, hygienic point of view, the zoölogical distribution of trichinosis extends to man, hogs, wild boars, rats, dogs, and cats. It is also reported for several other animals, such as the fox, etc., and has been transferred experimentally to several rodents (rabbits, hares, etc.) and other animals (sheep, cattle, etc.), but these exceptional infections or infections in animals not used for food do not enter largely into any scheme of prophylaxis.

[1] For zoölogical characters and a compilation of cases, see Stiles, 1907 *c*, *Bulletin No.* 34, Hygienic Laboratory.

[2] Synonyms.—*Taenia hirudinacea; Echinorhynchus gigas; Gigantorhynchus gigas; G. hirudinaceus; Hormorhynchus hirudinaceus.*

[3] Synonyms.—*Echinorhynchus moniliformis; Gigantorhynchus moniliformis; Hormorhynchus moniliformis.*

The Parasite.—Three stages of the parasite should be held in mind. (*a*) The *adults* live in the duodenum and jejunum; the males measure 1.4 to 1.6 mm. in length by 40μ in diameter, while the females are 3 to 4 mm. long by 60μ thick; they are circular on cross-section and appear as minute thread-like objects; *the œsophagus is supported by a single row of cells known as the cell-body;* the male is without spicules; the female is *viviparous*, the vulva being situated about one-fifth the length of the body from the mouth. The males die shortly after copulation. The females may remain for a few weeks in the lumen of the intestine, or they bore into the lymphatic spaces of the intestine where they live about five to seven to twelve weeks and deposit their numerous young, about 1500 or more per female, namely, the —

(*b*) *Embryos*, which measure about 90 to 100 μ in length by 6 μ in breadth; these wander, either with the lymph, or with the blood, less frequently actively, to the striated muscles. They begin to reach the muscle about the tenth day after infection; they enter the muscle fibres and there develop into the—

(*c*) *Encysted Larvæ.*—The cysts vary somewhat in size, but are usually about 400 by 250 μ. These encysted larvæ may remain alive in the muscles for years, cases being reported for as long periods as twenty to thirty-one years. The encysted worm (the "fleshworm") is the infecting stage, found in the hog; upon being swallowed in raw or rare pork, the cyst is destroyed, the larvæ pass from the stomach to the small intestine moult for the last time, and develop within about two days or less to the adults; the latter copulate and may have embryos in the uterus within less than a week after infection.

Source of Infection.—Leaving out of consideration rare exceptions, and considering only the usual methods, it may be said that (*a*) *man* obtains trichinosis from eating pork; (*b*) *hogs* become infected from eating (1) uncooked swill containing scraps of pork, (2) swine offal at country slaughter-houses, and (3) rats; (*c*) *rats* obtain their infection by eating (1) each other, (2) scraps of pork in houses or at meat-shops, and (3) swine offal at country slaughter-houses. Thus, rats alone, swine alone, or rats and swine together, can keep up an endless-chain infection, while the infection which reaches man terminates with the death of the individual. Accordingly, man must be viewed as a more or less accidental host, while the rat, because of its cannibalistic habits, presents, theoretically, ideal conditions to serve as a normal host.

Duration.—As a clinical combination of symptoms, trichinosis may last from a few days to several months, but usually it runs its course in about two or three to five or seven weeks; convalescence is slow and may require ten to seventeen weeks, while cases are recorded where the patients have not fully recovered from the effects for four to eight years. As an infection, on the other hand, it is reported as having lasted from five to twenty-four years in man and eleven to twenty-four years in the hog;[1] that is, cases are reported in which it is maintained that the encysted parasites have retained their vitality for these periods.

[1] It is not altogether clear that these records for twenty-four years must be accepted as absolute, for repeated infections might have occurred during these long periods.

Symptoms.—Incubation may last from several hours to several weeks, according to the amount of infection, and according to whether many parasites are ingested at one time, or whether consecutive infections of a smaller number of worms have occurred. Some infections are so light as to be entirely overlooked; other light cases, which might escape proper diagnosis, are recognized because of their contemporaneous occurrence with severe cases in the same family or among people trading with the same butcher. The more severe typical cases present Rupprecht's three more or less well-defined periods, corresponding to the three stages of the parasite and their respective location:

1. *Period of Ingression.*—The *adult* parasites are in the lumen or the tissues of the intestinal tract, hence gastro-intestinal symptoms predominate; but in some cases these may be absent or very slight. Within a few hours to two days or so, there is a more or less heavy feeling in the stomach, with eructations; nausea develops, and the patient may vomit once or several times, or in some cases persistently for some days; the appetite is diminished, constipation, or more generally diarrhœa, occurs, often with colic; the stools are at first fecaloid, but become looser even to an almost watery consistency; this diarrhœa may continue for some weeks or may give place to a more or less obstinate constipation. Muscular pains may develop early, even before the muscular tissue is invaded by the parasites; recurrent abdominal pains, especially at night, and as frequently as six attacks within twenty-four hours, may develop in the severest cases; the extremities become cold; the pulse small and intermittent. Toward the eighth day a *temporary first œdema* of the eyelids and face may appear lasting for from two to five days. From the seventh or eighth day on, large numbers of wandering embryos are found in the peritoneal, pleural, and pericardial cavities.

2. *Period of Digression.*—This begins on about the ninth or tenth or fourteenth day, rarely as late as the forty-second day (repeated small infections?), and corresponds to the *period during which the embryos are wandering and attacking the muscles;* accordingly muscular symptoms (myositis) are the most prominent. The symptoms may be exceedingly light to severe. Certain muscles, particularly the biceps and gastrocnemius, are more firm than usual, hard and very tender, especially when the patient extends the forearm or leg. Movement may cause excruciating pain, and for relief the patient assumes a position of semiflexion. Mastication, speech, and movement of the eyes become painful; more or less complete aphonia may occur and the eyes become fixed; respiration becomes difficult, and respiratory troubles are likely to be severe, especially in the fourth and fifth weeks; there may be severe dyspnœa, accompanied by violent asthma.

3. *Period of Regression.*—All symptoms become exaggerated, and in addition the patient falls into an extreme cachexia; *a second œdema* develops about the twenty-fourth day, occurring in about 90 per cent. of the cases and attacking the head especially; hence the name, "disease of the big head," occasionally applied to trichinosis in Europe. The *larval parasites encyst* and the patient gradually recovers.

This rather diagrammatic clinical picture varies according to the

amount and number of the infections. Early or late pruritis and formication may occur at certain points or over the entire body; cutaneous anesthesia is rare. Profuse sweating is likely to occur, especially during the myositis. Stiffness of the muscles of the neck and back, extending to a distinct opisthotonos, has been recorded. Thirst is increased. In females, anomalies occur in menstruation, and abortion is reported for some pregnant patients.

The urine decreases in quantity with the second week, but toward the fifth or sixth week and in convalescence there is polyuria. There may be an abundant sediment but the presence of *albumin is exceptional;* the urine may be intensely red in color.

As the nutrition is poor, extreme emaciation and anemia may develop, and there may be œdema of the lungs and an obstinate bronchitis. The mental faculties are dulled, and the patient is indifferent to what occurs in his presence. In severe cases more marked nervous symptoms develop—extreme insomnia or somnolence, delirium, etc. Opisthotonos, due to stiffness of the muscles of the neck and back, may be noticed. Even in light cases moderate *fever* may be present; in severe cases it appears during the stage of ingression; the temperature rises after the beginning of the muscular symptoms, often reaching 104° F., or even 105.8° F., its duration (two or three to five or six weeks) depending upon the severity of the infection; it may be remittent or intermittent. The *pulse* follows the temperature; in high fever it may exceed 100 and be extremely feeble. The skin not infrequently shows a miliary or roseolous eruption, more rarely herpes, and the œdema is frequently followed by extensive epidermic desquamation. Cancer of the tongue and lips has been reported as initiated by the trichinæ.

Lethality.—The death-rate is different outbreaks varies between 0 and 100 per cent. Of 14,820 cases in Germany collected by the writer for the years 1860-97, 831 were fatal, giving a death-rate of 5.6 per cent. The death-rate is low before the second and after the seventh week, and highest from the fourth to the sixth week, when the myositis is at its maximum.

Diagnosis.—In its severe form, trichinosis is a disease which occurs in groups of cases. In less extreme outbreaks cases may be mistaken for typhoid fever and "muscular rheumatism." The possibility of trichinosis should always be held in mind in case of the occurrence of several typhoid-like attacks in the same family or neighborhood, or among friends (especially Germans), and following a celebration at which pork was served, or among families trading with the same butcher. When trichinosis is suspected make the following examinations:

(*a*) Of the pork (if any has been left) to find encysted larvæ; if these be found, chop the pork finely, wash thoroughly in water to remove the salt, and feed immediately to two or three rabbits, guinea-pigs, or white rats in order to determine whether the larvæ are alive; never use wild rats or mice for this experiment; kill one animal after two or three days and examine the contents of the upper half of the small intestine for the adult worms; kill the second animal after two weeks, the third after three weeks, and examine the muscular portion of the diaphragm for the

larvæ. Even if live trichinæ are found in the intestine of the first animal, an examination of the second and third experiment animals may show that the parasites were too weak to reproduce to any extent, hence the prognosis is favorable.

(*b*) Upon the first suspicion of trichinosis, the patient's stools should be examined for discharged adult worms, especially if the diarrhœa is severe; dilute the fecal matter with warm water, using a rather tall, narrow graduate, or similar dish; shake well, filter through cheese cloth to remove the larger ingredients, replace in the graduate, and allow the worms to settle to the bottom; pour off any matter which floats; place the sediment in a shallow glass dish so that it will not be over $\frac{1}{12}$ inch deep, and, moving it gently over a dark background, by tipping the dish first to one side and then to the other, hunt for small hair-like objects which tend to cling to the glass (if the tipping is not too rapid); place these, if found, in a drop of water on a slide, cover with a cover-slip, and examine under a low-power lens.

(*c*) Examine the patient's blood for eosinophilia. The observation by Brown of the enormous increase in the eosinophiles has led to the recognition of many sporadic cases which otherwise would have been overlooked. Eosinophilia is contributory evidence but not proof of trichinosis.

(*d*) If in the third week or later and a diagnosis is not established but trichinosis is suspected, excise a minute piece of the patient's deltoid; tease this on a slide, add a drop of water, or water and glycerin, flatten gently by pressure on the cover-glass, and examine under low power to find the encysted worms.

(*e*) In case of death of patient, it is wise for the physician to fortify his diagnosis by clipping off a small portion of muscle from the underside of the tongue and examining this for trichinæ; the entire specimen should be properly preserved and marked for identification in court, as it will be of value in legally establishing the diagnosis.

Prognosis.—This is better in children than in adults, better in cases with severe diarrhœa in the early part of the disease, and good after the seventh week. If appetite, sleep, and respiration remain good, prognosis is good. Coma, delirium, and, in the last weeks, elevation of temperature and extreme dyspnœa are bad prognostic signs. Some patients recover in a few weeks; in others recovery is tedious, requiring months or several years.

Treatment.—If from the occurrence of a group of cases, or from a microscopic examination of meat, an immediate diagnosis is made, the stomach should be washed out. In case of an early diagnosis, but at a time too late to recover the ingested undigested pork or the worms from the stomach, purge the patient with calomel to remove as many of the worms as possible, for each female removed from the intestine means a reduction of the muscular infection by from 1500 to several thousand worms. Calomel has in addition some anthelmintic property. Thymol or beta-naphthol might be administered with good effect. The administration of anthelmintics has not been followed by very satisfactory results, the failure being due at least in part to the subepithelial

position of the females. No drug is known to kill the parasites in the muscles. After the parasites once leave the lumen of the intestine, all treatment must be symptomatic and supportive. Hot baths and morphine may be used to relieve pain; the profuse perspiration is relieved by atropine.

Prevention.—The German school favors a microscopic examination of pork before it is placed on sale, but statistics (Stiles, 1901) show that this system is not only very expensive but also open to many practical sources of error. Frequent suggestions are made that we should introduce this microscopic inspection into the United States. There are, however, numerous difficulties (legal, financial, practical, and theoretical) in the way of carrying out such a plan. It would cost, in the aggregate, five or more million dollars per year, and this sum of money could be spent to much better advantage in fighting tuberculosis or some other disease. The federal government could inspect the meat only at the registered abattoirs, and a system which has shown such poor results in Germany would certainly not appeal strongly to legislative bodies when the heavy appropriation was demanded. To inspect the pork in sparsely settled portions of this country is impracticable. Further, experience has shown that the microscopic inspection gives a false sense of security, and even in Germany the authorities have repeatedly felt it necessary to warn the public not to trust to the inspection, but to protect against the disease by thoroughly cooking the pork. If pork is thoroughly cooked or thoroughly cured, there is no danger of contracting trichinosis; and since cooking and curing are methods which appeal to American and English tastes, we can well urge these upon hygienic grounds also. The thermal death-point for the parasites is 55° C. (131° F.); for practical purpose of administration the U. S. Bureau of Animal Industry adopts a margin of safety at 58.3° C. (137° F.). Ransom has shown that refrigeration of trichinous pork at −15° C. (5° F.) for twenty days kills the trichinæ and is a practical measure when applicable. In the last analysis, the responsibility for trichinosis lies in the kitchen—not with the butcher—for pork is not a fit article of food unless and until it is properly prepared as food. An extermination of rats would result in a decrease of trichinosis.

Medico-legal Aspect.—Not infrequently, patients or heirs bring suit for damages against the butcher or the packer from whom the pork was purchased. The general line of procedure for the plaintiff's attorney is to attempt to prove that: (1) Meat eaten on a certain day was purchased from a certain meat shop to which it was supplied by a certain packer; (2) this meat was properly cooked; (3) shortly afterward, the consumers were taken ill; (4) the diagnosis was trichinosis; (5) the suffering was intense; (6) had the packer used proper precautions, he could have seen the trichinæ either by naked-eye examination or by microscopic inspection; (7) under common law, the meat was sold with an implied warranty that it was fit for food; (8) under the pure food laws, this meat was "diseased;" (9) damages are recoverable under 6, 7, and 8.

The technical reply is: (*a*) claims 2 and 4 mutually disprove each other, for if claim 2 be correct any trichinæ which might have been present must

have been killed, hence claim 4 is disproved by claim 2; or, if claim 4 be correct, the trichinæ were not killed, hence the meat was not properly cooked, ergo there was carelessness on the part of the plaintiff; (*b*) no method of inspection is known which can guarantee the absence of trichinæ from pork, hence to hold the butcher responsible for the presence of trichinæ in his pork is unreasonable; (*c*) in view of *b*, either cooking or freezing is the reasonable method of preventing trichinosis; (*d*) freezing is not universally applicable (unreasonable expense, hence unreasonable prices for pork, etc.) but cooking is; (*e*) momentary exposure to the thermal death-point kills the parasite and this temperature is reached in thorough cooking; (*f*) the word "diseased" is used in many senses, and if in the interpretation of the pure food laws this term is made to include all parasitized meats and parasitized animals, it practically excludes all meat from the food market; a reasonable interpretation of the word would be that the disease is communicable to man; dead trichinæ are not dangerous; (*g*) the implied warranty in the sale of foods becomes unreasonable unless predicated upon the premise that the food is to be prepared properly before being eaten (compare oysters in the shell, unplucked fowl, unswollen beans, etc.); (*h*) as proper cooking is the only generally applicable means of preventing trichinosis, the seller cannot be held responsible if trichinosis develops unless it be granted that he has the right to oversee the cooking but this would presuppose the right of search without warrant. In summary, the cook—not the butcher—is the person upon whom the responsibility falls, if trichinosis develops.

Innocent lack of technical information in regard to the public health aspects of trichinosis has resulted in some rather remarkable expert testimony, and physicians who testify in cases of this kind will do well not only to fortify their diagnosis, but also to examine the records of the practical results of microscopic inspection for trichinæ before they testify in support of its value.

Some court decisions in reference to liability are based not upon the medical testimony but upon the principle of general customs of the trade —for instance, butchers do not inspect for trichina, accordingly, this inspection is not a standard trade-custom, hence butchers are not guilty of carelessness if they fail to inspect the pork microscopically.

Pseudotrichinæ.—Various parasites have been mistaken for trichinæ. Thus a sarcosporidium (*Sarcocystis miescheriana*), which is exceedingly common in pork, has been repeatedly mistaken for trichinæ, but the fleshworm is usually wound in a spiral and enclosed in a much thicker cyst, while the *Sarcocystis* is more elongate, slender, straight, and with content that appears granular under the microscope; under high-power magnification, these granule-like bodies are seen to be more or less crescentic in form, somewhat similar to the crescents of estivo-autumnal malaria. The worms described as *Trichina affinis, T. agilissima, T. anguillae, T. cyprinorum, T. cystica, T. inflexa, T. lacertae* and *T. microscopica,* from various animals, are not *trichinæ.* Various strongyles have been recorded as trichinæ. An interesting case of pseudotrichinosis is presented in *Rhabditis terricola* (*R. cornwalli, Pelodera setigera*). This nematode was found in an exhumed cadaver of an English cadet, from the

ship Cornwall, and was mistaken for a trichina; on the basis of this erroneous zoölogical determination, the outbreak of disease was pronounced trichinosis and attributed to American pork.

PULMONARY ROUNDWORMS

Metastrongylus apri (Gmelin, 1790) is a 12 to 50 mm. long threadworm, which is rather common in the lungs of hogs. It has been reported by Diesing (1851 *a*, 317) once for the lungs of man; Chatin (1888 *b*) states that it also occurs in the stomach of man, but such cases are probably due to eating hogs' lungs containing the worms. Rainey's (1855) case of *Filaria trachealis* in the trachea and larynx of a human subject may possibly belong under *M. apri*. The eggs of *M. apri* measure 50 to 100 by 37 to 72 μ, and contain an embryo at oviposition.

SUBCUTANEOUS ROUNDWORMS

Gnathostoma spinigerum (Owen, 1836) is a very remarkable nematode which has been collected on several occasions from similarly affected patients in Siam, and China. It attains 9 mm. in length by 1 mm. in breadth; head globular, with 8 circles of simple spines; mouth with two lips; anterior third of body with scale-like, tridentate spines, which become smaller and more simple the farther they are from the head. The brief description by Levinson is based upon a female parasite collected from a Siamese in a superficial nodule on the side of the chest. This parasite is found in the stomach of dogs and tigers and its occurrence in man is abnormal. *G. siamense* Levin., 1890, is accepted as a synonym.

G. hispidum (Fedsch., 1872), of swine, is reported as one of the causes of creeping disease (dermatitis linearis migrans) of man in Japan.

Rhabditis niellyi (Blanchard, 1885) is at present a nominal species which can scarcely be classified, even generically, with any degree of certainty. It is known only as a rhabditiform larva, 333 μ long by 13 μ broad, which was found by Nielly (1882 *a*) in cutaneous papules, chiefly on the limbs, in a boy at Brest; small worms were also found for a time in the blood, but examination of the feces, urine, and sputum was negative. Authors have compared this case with craw-craw, and have explained the infection upon the assumption that the boy might have swallowed eggs in drinking water of poor quality; that the embryo then escaped and reached the blood and skin. Possibly an equally plausible explanation would be to assume a direct cutaneous infection after the manner of uncinariasis. Whittles (1903 *a*) reports a case of hypertrophic gingivitis in a female, aged nineteen years, in whom small nematodes were found in the periosteum of the upper jaw after tooth extraction· the worms were also found elsewhere, as in abscesses in the skin.

Lagochilascaris minor (Leiper, 1909), has been reported in 2 cases of subcutaneous abscess in man in Trinidad. The question has been raised as to whether these do not represent cases of deception on the part of the

patient. The males were 9 mm., females 15 mm. long; small interlabia present; the lateral membrane is not confined to the head but extends the length of the body; vulva with two salient labia, 3 mm. from head.

Dracunculosis[1] **or Guinea-worm Infection. Geographical Distribution.**—This is essentially an Old World infection, being endemic in India, Persia, Turkestan, Arabia, and certain parts of Africa. It was introduced into South America by the slaves, but does not appear to have flourished there to any great extent. Occasional imported cases are reported in other parts of the world, several being recorded for the United States (Francis, 1901 *a*, and others).

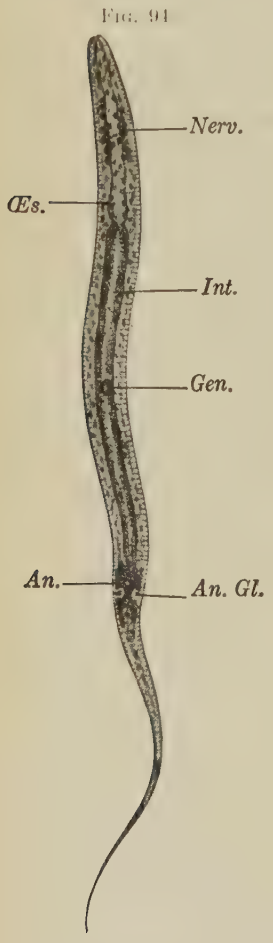


Fig. 94

Embryo of the Guinea-worm. *Nerv.*, nervous system; *Œs.*, œsophagus; *Int.*, intestine; *Gen.*, genital primordium; *An. Gl.*, anal papillæ of glandular nature. × 190. (Looss.)

Zoölogical Distribution.—This parasite is reported also for cattle, horses, dogs, and several wild animals. Manson has suggested that possibly some of these cases represent specifically distinct infections.

The Parasite.—The Guinea-worm or Medina-worm, *Dracunculus medinensis* (Linnaeus, 1758), is a white to yellowish parasite, 30 to 120 cm. long by 0.5 to 1.7 mm. in diameter; its anterior end is bluntly rounded, with a small terminal mouth and 6 papillæ. A vulva has not positively been discovered; possibly the genital organs discharge through the œsophagus. The intestine is rather reduced and no anus is present in adult specimens. The uterus is enormously developed and filled with sharp-tailed embryos 0.5 to 0.75 mm. long by 15 to 25 μ in diameter.

Source of Infection.—The embryos escape, possibly through organs prolapsed through the mouth of the adult worm, and may live in clear water for six days, in muddy water or moist earth two to three weeks; if slowly dried, they resuscitate in water. They may enter small crustaceans (*Cyclops bicuspidatus*, *C. coronatus*, etc.), and within about three weeks develop to 1 mm. in length, casting the skin, losing the long tail, acquiring a cylindrical shape, and developing a tripartite arrangement on the tip of the tail. They are then swallowed in the drinking water. It was formerly believed that the worm entered through the skin, and, as this mode of infection is demonstrated for certain other worms, doubtless the possibility of this method will again be considered in connection with this species. The further history to the gravid condition, has not been followed, but probably the worms soon leave

[1] Synonyms,—Dracontiasis; Guinea-worm disease,

the intestinal canal and reach the connective tissue; after copulation the male probably dies, while the gravid female, about ten to fourteen months after infection, wanders to the subcutaneous tissue.

Symptoms.—The gravid parasite produces very painful, superficial, furuncle-like swellings, chiefly on the feet and legs (about 85 per cent. of the cases), and occasionally on other parts of the body, as the back, neck, head, wrist, scrotum, penis, etc. A small blister forms and elevates the epidermis; the blister ruptures, disclosing a superficial ulcer about $\frac{3}{4}$ inch in diameter, at the centre of which there is a small opening about 2 mm. in diameter, from which the head sometimes protrudes. There may be fever, chill, nausea, and vomiting. The swelling may last two or three weeks; then the worm is extruded and the wound heals; or premature death of the parasite may give rise to an abscess; or the worm may become calcified and be felt for years as a hard knot.

Treatment.—Emily's (1894 *a*) treatment consists in injecting bichloride of mercury (1 to 1000) into the protruding worm, which can then be easily removed twenty-four hours later; or if the worm itself is not visible, a few drops of the solution are injected as near the coil as possible; the parasite may then be wound out or cut out. Another method is to protect the infected part from injury and douch it frequently with water; when this is done the uterus gradually empties and the worm may be extracted or it may come out of its own accord. Traction should not be used so long as the parasite discharges embryos, which may be determined by microscopic examination of the fluid issuing from the opening. The old method of extraction is to pass a coil of the parasite through the cleft end of a small stick and to wind it out of the wound *very* slowly, making only one or two turns of the stick daily. The objection to this method is that the worm sometimes breaks, the embryos escape into the surrounding tissue; violent inflammation ensues, with fever, abscess, and sloughing, and weeks or months may elapse before the patient recovers; death may occur from septic infection. Cummings (1910) prefers gradual traction to the perchloride method.

Prevention.—Upon the premise, based upon experimental evidence, that the infection takes place through swallowing *Cyclops* in drinking water, only filtered or sterilized water, or water of unquestionable origin should be taken when in an infected region.

Onchocerca caecutiens Brumpt, 1919, of Guatemalan coastal erysipelas, lives in tumors which are subdermal, intramuscular, and even periosteal (producing perforation of the cranium). The males measure 24 to 42 mm., the females up to 50 cm. in length, by 190 to 300 μ in diameter; the embryos 250 μ long, are without sheath and are not found in the peripheral circulation. "Sand-flies" (*Simulium samboni*, *S. dinelli*) have fallen under suspicion as intermediate hosts. Development in man appears to be very rapid, as cases of these worm tumors are reported in persons three months after their arrival in the endemic area. The infection results in two rather distinct conditions: (1) Cutaneous onchocercosis, or coastal erysipelas (acute or chronic), and (2) ocular onchocercosis (with chronic superficial punctate keratitis lasting several years and resulting in blindness). Medicinal treatment, thus far, is unsatisfactory, but complete

surgical removal of the worm-tumors is reported to result in amelioration within a few hours and complete cure in a week.

Onchocerca volvulus Leuckart, 1893, is found in subcutaneous tumors, in patients in West Africa. The male measures 30 to 35 cm. long, and has two unequal spicules, 82 and 177 μ long; tail strongly incurved. The female measures 50 to 70 cm., and is viviparous; vulva 850 μ from mouth. The embryos are 250 to 300 μ by 5 to 7 μ, without sheath, and with sharp tail; these have been found in tumors, but not in the blood. According to Labadie Legrave (1899) the worm is in a lymphatic canal. The life cycle has not been demonstrated, but *Microfilaria nuda* Rodenwaldt is under suspicion as the young form and *Glossina palpalis* as a doubtful vector.

Infection with the Loa.—Geographical Distribution.—This infection is known particularly for the west coast of Africa, but imported cases are reported for other localities, chiefly in slaves or in missionaries who have visited Western Africa. Ward (1906) collected the recorded cases and published several new cases for North America.

Zoölogical Distribution.—The loa is known positively only for man, but Blanchard states that according to Plehn (1898) the natives say it also occurs in sheep and goats.

The Parasite.—*Loa loa*[1] (Cobbold, 1864) is a filiform, colorless to yellowish-white threadworm, 16 to 57 mm. long by 0.3 to 0.57 mm. in diameter; the cuticle is not striated but is provided with numerous wart-like structures; male with lateral caudal alæ; 3 or 4 pairs of preanal pedunculated papillæ, decreasing in size from the anterior to the posterior, and (1 or) 2 or possibly 3 pairs of smaller postanal papillæ; spicules unequal, up to 113 and 176 μ long, average given as 88 and 123 μ; vulva of female 2.35 to 2.5 mm. from head; viviparous. The embryo, *Microfilaria diurna*, circulates in the peripheral blood during the day.

Source of Infection.—Manson suspected that mangrove flies (*Chrysops*) act as intermediate host and confirmation of this view has been published (Leiper) for *C. dimidiatus* and *C. silaceus*.

Duration.—*Loa loa* is apparently rather long-lived; it has been seen in persons who had been away from the infectious locality for from four to eleven years.

Symptoms.—This parasite inhabits the connective tissue all over the body, which it traverses freely; observations indicate that it is quite superficial; it is seen especially around the eye in the subcutaneous fascia about the orbit, between the conjunctivæ and bulbus; it travels over the nose, in the fingers, penis, etc. It disappears from the surface in two or three days and reappears after some days, weeks, or months. Its appearance is favored by warmth and retarded by cold.

The loa causes an itching, creeping, prickling sensation, with occasional œdematous swellings and in some cases lacrimation or considerable pain; it may determine a more or less intense conjunctivitis and disturbances in vison. Several authors have associated with loa infections the so-called "Calabar swellings" and "Kamarunbeulen;" these appear suddenly on various parts of the body as elevations about one-half the size

[1] Synonyms.—*Filaria oculi*, 1859; *Dracunculus oculi*, 1860; *D. loa*, 1864; *F. loa; F. subconjunctivalis*, 1864; *F. diurna; F. sanguinis hominis major; F. sanguinis diurna; F. bourgii.*

of a goose-egg, or 40 to 60 mm. in diameter, they wander slowly, about 20 to 30 mm. per day, then disappear in about three days to reappear after some months or years; they are painless, but slightly irritating; do not pit on pressure, and feel "somewhat hot both objectively and subjectively;" they may occur on any part of the body, but, according to one patient, are caused by rubbing or scratching to relieve the irritation produced by the worm.

Treatment.—When the loa approaches the surface it can readily be seen beneath thin skin as in the eyelid or over the bridge of the nose. It is then secured by means of forceps, an incision is made, and a second pair of forceps used directly on the worm; the first pair of forceps is released and the worm drawn out with the second pair. The natives extract the parasite with a sharp thorn, or drive it into the deeper tissue by dropping a grain of salt into the conjunctival sac. The injection of bichloride of mercury (1 to 1000) when the worm appears in parts of the body other than near the eye has been done.

Agamofilaria georgiana Stiles, 1907, is an immature worm of uncertain systematic position, found in a superficial sore on the ankle of a negress in Georgia. It measures 32 to 53 mm. long by 560 to 640 μ in maximum diameter and its mouth is surrounded with 2 small lateral papillæ and 4 large submedian lip-like papillæ.

FILARIASIS

Infections with Threadworms of the Genus Filaria.—The genus *Filaria* Müller, 1787, includes long, slender, filiform threadworms with curved or spiral tail. The male is smaller than the female, has 2 unequal spicules, 4 preanal papillæ, and a varying number of postanal papillæ; in the females the vulva is near the anterior end. The adults are parasitic, especially in the connective tissue, lymphatics, and body cavities; the embryo or larva frequently inhabits the blood, and in several species for which the life history is known, insects such as mosquitoes form the intermediate host. The genus *Filaria* has been divided into a number of distinct genera, so that a change of technical names in unavoidable.

Three stages of filariæ occur in man, namely: (*a*) An *embryonic* stage (known as *Microfilaria*) which usually occurs in the blood and is the stage of transmission to the intermediate hosts (insects, crustacea) in which it develops into the *larva* which the intermediate hosts transmit back to man; the larva develops into (*b*) an *immature stage* (known as *Agamofilaria*) without sufficiently formed organs (especially genitalia) to permit of a generic determination; this agamic stage develops into (*c*) the *adult* with developed genitalia which permit of a generic determination. Certain adult filariæ which occur in man have been eliminated from *Filaria*, s. l., and classified in the genera *Dracunculus* (type *medinensis*), *Loa* (type *loa*), *Onchocerca* (type *reticulata*, of horses), *Wuchereria* (type *bancrofti*), *Dirofilaria* (type *immitis*, of dogs), *Setaria* (type *equina*, of horses), and *Acanthocheilonema* (type *dracunculoides*, of the Aard-wolf). *Filaria*, sensu stricto, has for its type *F. martis*, of martens, and it is not definitely known that any filaria, s. l., of man belongs in the genus *Filaria*,

s. str. Several species described for man are not yet classified under the modern generic conceptions and are therefore quoted under the older conception of *Filaria*, s. l. This indefinite nomenclature for these forms cannot be avoided; but it can be minimized by use of *sensu lato* after the generic name, as *Filaria*, s. l. or by adopting "(*Filaria ?*)."

Quite a number of species are reported as parasitic in man, but not all of them are described with sufficient accuracy to permit a positive zoölogical determination. In medical literature the chief interest has centred around the so-called *Filaria sanguinis hominis*. As a matter of fact, the name *Filaria sanguinis hominis* means but little more than does the expression "the tadpoles of Virginia." In recent years *Filaria sanguinis hominis* is becoming confined more and more to one species, namely, to *Filaria bancrofti;* but as a scientific name it should be eliminated from medical literature. The reliable determination of the various species of *Microfilaria* has become so complicated that it is essential to consult the special parasitological literature for detailed data. Accordingly, mere indications of some of the forms will be given here.

So far as has been proved none of the *Microfilaria* does any appreciable injury in the blood, and of the adult worms only one, namely, "*Filaria bancrofti*," can at present be viewed as serious both as respects damage and frequency; all other filariæ of man are to be considered as trivial in comparison.

Infection with Filaria (seu Wuchereria) bancrofti.—Geographical Distribution.—Australia is the type locality for this parasite, but it may be designated in general terms as a tropical and subtropical infection. It is especially common on the east coast of Africa, in South China, certain parts of India, Samoa, Friendly Islands, West Indies, etc. In the United States cases are occasionally found in the Southern States; Mobile (Anderson); Charleston, S. C. (Guiteras and others); occasional cases are found farther north.

Zoölogical Distribution.—The adult worm is thus far known only for man.

The Parasite.—Bancroft's filaria[1] (*Filaria* (seu *Wuchereria*) *bancrofti* Cobbold, 1877) is a whitish or brownish, (?) transversely striated worm, 44 to 100 mm. long by 0.1 to 0.30 mm. in diameter; male with two spicules, 0.2 and 0.6 mm. long, anogenital pore 138 μ from tail, preanal papillæ uncertain, but apparently 15 pairs of postanal papillæ; vulva of female 0.66 to 0.75 (or 1.2 to 1.3 mm.) from head, anus 225 to 280 μ from tip of tail. Viviparous. The embryos, 300 to 340 μ long by 6.6 to 8.5 or 11 μ in diameter, are found in the circulating blood and are provided with a sheath and sharply-pointed tail; they show a more or less marked periodicity in that they are much more numerous in the peripheral circulation during the night; but if sleep is reversed to daytime, the periodicity also is reversed. Mosquitoes, while biting patients, swallow these embryos, which then undergo development in the muscles, and finally, after six to nineteen

[1] Synonyms.—*Filaria sanguinis hominis* (a dead name) embryo; type locality, Calcutta (Lewis). *F. dermathemica* (1875); type locality, Bahia. *F. bancrofti* Cobbold, July 14, 1877*g;* adult; type locality, Australia. *F. wuchereria*, 1877; type locality, Brazil. *Wuchereria filaria. F. nocturna*, embryo.

days, or, by lower temperature, up to thirty-five or forty-one days from time of infection, the worms reach a stage (ca. 1.7 mm. long) in which they are transmitted to man during the bite by the mosquito.

Nothing is known of the biology of the worm from the time it enters man up to the adult stage. The adult worms occur alone or as several coiled together, chiefly in the lymphatics, but also occasionally in the fluids in swollen organs. There is no satisfactory explanation, as yet, of the periodicity shown by the larva.

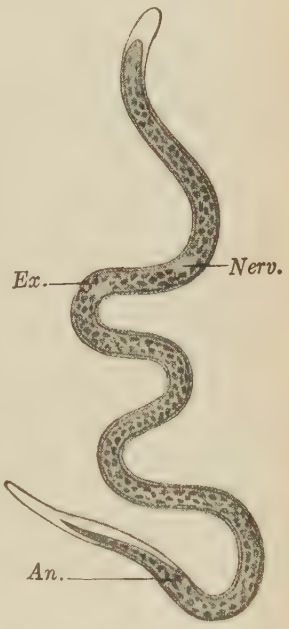
Source of Infection.—Various mosquitoes (*Anopheles, Culex, Stegomyia*).

Frequency.—This varies with exposure to infected mosquitoes. In some places the infection is rare; in others it increases to 5, 10, 20, 50, or more per cent. of the inhabitants.

Duration.—Nothing positive is known regarding the longevity of the adult or larva, but apparently neither is very short-lived.

Symptoms.—That numerous cases of infection show no appreciable symptoms is well established, but that in other cases the worms produce serious results must be admitted, especially if the adult parasites are present in large numbers or unfortunately located. According to Manson, *Filaria bancrofti* may produce the following conditions: Abscess, lymphangitis, varicose groin glands, varicose axillary glands, lymph scrotum, cutaneous and deep lymphatic varix, orchitis, chyluria; elephantiasis of the leg, scrotum, vulva, arm, mamma, etc.; chylous dropsy of the tunica vaginalis, chylous ascites, and chylous diarrhœa. In not all of these cases is the method by which the parasites do harm fully understood, and the relation of the parasites to elephantiasis is based chiefly upon circumstantial evidence. In general, the adult parasites, or, Manson believes, in some cases, "their immature products of conception," cause two principal types of filariasis, one characterized by a varicosity of the lymphatics, the other by a more or less solid œdema.

FIG. 95



Larva of *Filaria bancrofti* in the blood of man in Egypt. *Nerv.*, nervous system; *Ex.*, excretory; *An.*, anus. × 514. (Looss.)

The frequency of these various manifestations does not seem to be uniform in filarial patients in different geographical areas, but the reason for this variation is not at present clear.[1]

Filarial Abscess.—These may be present in various affected organs and may contain the dead adult worms. They may discharge or be opened; if in the thorax or abdomen they may be serious. According

[1] Is it possible that local conditions, incident to the geographical distribution, have resulted in differentiating *F. bancrofti* into several subspecies, each with special tendency to a given clinical manifestation? Or have we in man even a larger number of distinct species of *Filaria* than have yet been described?

to Manson, deep-seated pain in the thorax or abdomen, with inflammatory processes followed by hectic fever and a diminution in the number of or disappearance of filaria larvæ in the peripheral blood, suggest filarial abscess, and indicate exploration, and, if feasible, operation.

Lymphangitis.—Elephantoid Fever.—This is common in all forms of filariasis due to *F. bancrofti;* it may or may not be followed by more severe conditions, as elephantiasis, lymph scrotum, varicose glands, etc. It usually appears on the extremities, but may be confined to other parts (groin glands, testis, spermatic cord, or abdominal lymphatics). The attack continues for several (usually two) days, then may recur after weeks, months, or years. It begins with a severe and prolonged chill (rigor), followed by high fever, 105.8° F.; is accompanied by headache, loss of appetite, frequent vomiting, and even delirium; it ends with profuse perspiration. At the onset of lymphangitis of the extremities, the painful cord-like swelling of the lymphatic trunks and of their glands, with a red, congested streak in the overlying skin, is visible; abscess or gangrene may develop; finally the tension is relieved by lymphous discharge and the swelling partially subsides, but the skin and subcutaneous tissue do not return to their normal condition, some permanent thickening remaining. Elephantoid fever has been repeatedly mistaken for malaria, but a differential diagnosis should not be difficult. The filaria embryos are not always found in the blood. In *treatment* elevate the affected part with absolute rest; give a milk diet; use mild laxatives, cooling lotions or warm fomentations, opium to relieve pain, and scarify the swollen area if necessary to relieve tension.

Varicose Groin Glands, Helminthoma Elasticum.—These frequently accompany lymph scrotum but may occur with other filarial manifestations; the affection may be unilateral or bilateral. They are soft, doughy, obscurely lobulate, and stationary in position; but the skin may be readily moved over them. They may be easily mistaken for hernia. If the patient lies with raised pelvis the swelling slowly disappears; but if he stands erect the swelling slowly returns while the hand is pressing against the saphenous or inguinal opening. The contents are white to red, chylous, rapidly coagulable fluid, and usually contain filaria embryos. This condition is frequently mistaken for hernia, but the swellings are not tympanitic on percussion; upon pressure they disappear slowly, and there is no gurgling; there is little or no impulse on coughing. Manson emphasizes the fact that chronic swellings about the groin, cords, testes, and scrotum in patients from the tropics should always be regarded as of possible filarial origin. They are best left alone unless they result in an incapacitating discomfort, when they may be removed. Operation is not always satisfactory, as it may be followed by lymphorrhagia, excessive dilatation of some other part of the lymphatic area, chyluria, or elephantiasis. Godlee, to prevent lymph stasis, drained the lymphatics of the region operated on into the vena spermatica and v. saphena, obtaining good results.

Lymph Varices.—These are not rare, and may be superficial on the abdomen, legs, or other parts, or may be more deeply located. If they rupture, lymphorrhagia results. They may appear and disappear within a few hours, and indicate lymphatic obstruction.

Lymph Scrotum.—This is frequently accompanied by varicose groin and femoral glands. The skin is silky to the touch, but represents lymphatic varices which may open and discharge milky to bloody, rapidly coagulating lymph, usually containing filarial embryos, which are also present in the blood. Elephantoid fever probably results from external mechanical irritation; the scrotum may become thickened, and elephantiasis may develop. In treatment, support and protect the scrotum, which should be kept clean and powdered; but otherwise leave it alone unless inflammation be frequent, debilitating lymphorrhagia be present, or elephantiasis develops. If operation is decided upon, excise all the diseased tissue, obtaining flaps from the thigh if necessary. The patient should be warned of the possible occurrence of chyluria or of elephantiasis of the leg as a result of this surgical interference.

Chyluria; Hematochyluria.—This is common, but intermittent; it may appear without warning or be preceded by pains in the back, pelvis, and groin; the first symptoms may be retention of urine due to chylous coagulation in the bladder; the color of the discharge varies from a milky-white to a blood tinge, not only in different cases but also in the same case. It is rarely continuous; attacks occur usually lasting weeks or months or up to two years (Sheube), with more or less prolonged intervals. While not directly dangerous, the continued drain may result in anemia, debility and incapacity for active life. Attacks are favored by pregnancy, childbirth, running, and other violent exertions which lead to rupture of a lymphatic varix in the bladder wall.

Treatment consists in absolute rest in bed, with elevated pelvis, a light saline purge, vesical irrigation, and restriction of food (especially fats) and fluids. The value of any drug treatment is doubtful. Filarial embryos may be numerous in the urine.

Orchitis.—This occurs as an acute manifestation accompanied by headache and vomiting, and disappears as rapidly as it appears. It is preceded by elephantoid fever; there is a very rapid and very painful inflammation of the testes, which are much swollen; the swelling may also involve the epididymis, spermatic cord, and entire scrotum. Afterward, the fluid in the tunica vaginalis may not be entirely absorbed but may lead to chylocele. Filariæ are often present in the blood. Manson suggests the possibility that the "malarial orchitis" of certain authors may in reality be a filarial orchitis.

Chylocele.—This manifestation is more or less common, either alone or more frequently with or as a result of varicose lymph glands, lymph scrotum, etc. In the morning it is always soft and it is never so tense as common hydrocele. Numerous filarial embryos are present in the milky, reddish, quickly coagulating content. Treatment is identical with that of ordinary hydrocele.

Arabian Elephantiasis.—The recurring attacks of elephantoid or erysipelatoid fever, with resulting and accumulative thickening of the affected part, gradually give rise to an elephantiasis, which, according to Manson, is the most frequent manifestation of this filarial infection. Occasionally, progressive elephantiasis occurs after only one or several attacks of elephantoid fever. It is estimated that in 95 per cent. of the cases, the

elephantiasis occurs in the legs, either alone or with elephantiasis of the scrotum or arms. Elephantiasis of the scrotum is common, while that of the arms, mammæ, vulva, and limited areas (pedunculated elephantoid tumors) is more rare. In only a proportion of the cases are the filariæ found in the blood or in the fluid of the diseased organ.

The skin is rough and coarse, the hair is coarse and sparse, and the nails thick and deformed. The part pits but slightly or not at all on pressure, and does not glide over the underlying tissues. The skin is dense, fibrous, and enormously hypertrophied; the connective tissue is hypertrophied and "blubbery" from its infiltration with lymph; blood-vessels are large; the lymphatics are dilated and the lymphatic glands enlarged. As even slight injury to the affected part may induce a recurrence of the elephantoid attacks, care must be taken to protect it. Violent exercise, exposure to the hot sun, etc., should be avoided. Massage, elevation of the affected part to drain out the lymph, and elastic bandaging, are useful. Absolute rest in the recurrent attacks of fever should be insisted upon; permanent recovery never occurs.

In extreme cases of *elephantiasis of the leg*, good results are sometimes obtained by excising a longitudinal strip 3 to 4 inches in breadth by 12 or more inches in length; during the febrile attacks, tension may be relieved by punctures with a lancet under aseptic conditions.

Elephantiasis of the scrotum frequently develops to tumors of 10, 20, 40, or 50 pounds; Manson gives 224 pounds as the largest case on record. These growths are unsightly and inconvenient, but not, as a rule, directly dangerous. Occasionally they endanger life by becoming gangrenous or by abscess formation. They may develop rapidly, in two or three years, or very slowly. Upon reaching such a size that they are unsightly or inconvenient, surgical interference is indicated.

For *elephantiasis of the arm*, massage and elastic bandaging are used.

A number of authors doubt whether elephantiasis is due to *Filaria bancrofti*. The general weight of circumstantial evidence seems, however, to indicate that at least some cases are due to this cause, while other cases which might formerly have been attributed to this worm may perhaps be due to other causes—as streptococcus infection. Brault recognizes a bacterial (streptococcus) and a filarial elephantiasis.

Diagnosis.—An attempt should always be made to find the embryonic filaria in the blood, urine, or chylous accumulation. There are chances for error in connection with the examination of the urine, and probably all those cases in which eggs are reported for the urine should be definitely rejected. *Trichina cystica* Salisbury, for instance, which nearly all authors have identified with *Filaria bancrofti*, is doubtless *Enterobius vermicularis;* vinegar eels (*Anguillula aceti*) have also been mistaken for filariæ. *Blood:* The lymphocytes increase to 24 to 40 per cent.; the eosinophiles to 8 to 18 per cent.

Prognosis.—While filariasis is a disease which cannot be absolutely cured, the prognosis in uncomplicated cases is reported as good. Even in severe infections life may not be in danger.

Treatment.—Treatment to exterminate the larvæ in the blood is not only rather unsuccessful but also unnecessary. Authors have claimed

that they may be reduced in numbers with thymol, ichthyol, etc. The writer takes exception to the view that such treatment is undesirable, if found to be practicable, as eradication of the embryos is naturally an important point in prevention. Anthelmintic treatment, directed against the adult, is not only useless, but possibly undesirable, as the dead worm is viewed by some authors as more dangerous than the live parasite.

The symptomatic treatment consists in rest, lowering the tension of the lymphatics by saline purgatives, by appropriate food, and limitation of fluids ingested. Several drugs (potassium iodide, gallic acid, methylene blue, etc.) have gained a temporary reputation, but probably their administration accidentally coincided with the time of spontaneous remission. The necessity for asepsis in operation is self-evident. Manson advised postponement of operation so long as convenient, but some authors are less conservative on this point.

Prevention. — Every person with filaria embryos in the blood, whether any pronounced symptoms are present or not, should, because of the danger of spreading the infection by mosquitoes, be considered a danger both to himself and to others. This danger can be checked by compelling him to sleep under a mosquito-net.

Filaria taniguchii Penel, 1905, is reported as 68 mm. long (female), 0.2 mm. in maximum diameter; the vulva is 1.3 mm. from the mouth, the anus 0.23 mm. from caudal end; cuticle very finely striated; anterior end with 2 pairs of buccal papillæ; eggs 40 by 25 μ pointed at each pole; embryos in utero measure 290 μ long by 7 μ in diameter without sheath. The adult is found in the lymphatic ganglia. Male unknown. The embryos show a nocturnal periodicity in the peripheral blood; they measure 164 μ long by 8 μ in diameter; a sheath is present, the tail is truncated. Type locality, Ama Kusha, Japan. The fact that both a sheathed and an unsheathed embryo are ascribed to this species suggests the possibility that some confusion may have occurred. The adults live in the lymphatics and play the same role as *Wuchereria bancrofti*, q. v., with which Tanaguchi, 1903, identified them.

Acanthocheilonema perstans (Manson, 1891) was based upon filarial embryo (see p. 599) found in West Africa in the peripheral circulation both night and day. Adult worms, 35 to 80 mm. long, have now been found in the mesentery and elsewhere, which are accepted as the adult stage. The male is said to have 4 pairs of preanal and 1 or 2 pairs of postanal papillæ; in the female, the vulva is 0.6 to 1.2 mm. from the mouth, the anus 0.145 mm. from the tail. The head in both sexes is large and the tail is described as having 2 minute triangular projecting appendages, giving it a mitered appearance. This parasite is reported for Africa and South America. This species has been reported in the chimpanzee also. The worm is supposed to be non-pathogenic. The life cycle is not known, but two mosquitoes (*Anopheles maculipennis* and *Taeniohynchus fuscopennatus*) are under suspicion as vectors.

Filaria ozzardi Manson, 1897, is reported for connective tissue in British Guiana and St. Louis; the worms are 38 to 81 mm. long; male without (?) any caudal papillæ; in female, vulva 0.71 mm. from mouth, anus 0.23 mm. from tail. Embryos (see p. 599) in peripheral blood night

and day and can at least begin further development in *Stegomyia aegypti*. This species is interpreted by Brumpt as including *F. demarquayi* 1897 (not 1891) and *F. juncea*, 1908.

Filaria juncea Railliet, 1908 (syn. *F. demarquayi* Manson, 1897, not Zurne, 1891) is a threadworm which has been reported for St. Vincent, West Indies (type locality), St. Lucia, Dominica, and Trinidad. The female measures 65 to 80 mm. long by 0.210 to 0.250 mm. in diameter; the vulva is 0.76 mm. from the mouth; anus 0.25 mm. from the tail; it lives in the subperitoneal connective tissue and is known only for man. The embryo lives in the blood, is 200 to 210 μ long by 5 μ in diameter, without sheath; the tail is sharply pointed; movements are very active; they do not exhibit any daily periodicity. The life history is unknown and experiments on mosquitoes have thus far been negative. Wellmann believes that a tick (*Ornithodoros moubata*) is the intermediate host. This worm may be identical with *F. ozzardi*.

Dirofilaria magalhāesi Blanchard, 1895, has been found but once, in the left heart of a child in Rio de Janeiro. The male is 83 mm. long; with 4 preanal and 4 postanal peculiar papillæ with scalloped outline; shorter spicule 0.17 to 0.23 mm. long, longer spicule not measured; female 155 mm. long; vulva 2.56 mm. from head; cuticle with transverse striation. Nothing is known regarding the life-history or medical importance of this worm.

Dirofilaria immitis Leidy, 1856, is a 12-to-30-cm. long threadworm found in the right half of the heart of dogs. Mosquitoes (*Anopheles* and *Culex*) form the intermediate host. Bowlby is said to have reported its presence in the portal vein of man, but the zoölogical determination is open to question. It has been claimed that the worm in question was undoubtedly a blood fluke (*Schistosoma haematobium*).

Setaria equina (Abildgaard, 1789) is a more or less common parasite in the abdominal cavity, occasionally in the pleural cavity, liver, skull, and elsewhere, of horses and asses; and several cases of its accidental presence in man have been reported. (Pleural cavity, Linstow, 1902; bronchial glands, *Filaria lymphatica* Treutler, 1793; Brera, 1811; Blanchard, 1890*a*, 16.) The parasite measures 6 to 22 mm. long, and has a very characteristic blunt cephalic end, provided with two lateral semilunar structures. Its life-history is not known.

(? Filaria) kilimarae Kolb, 1898, is at present a nominal species (type locality Kilimara, British East Africa). It attains 10 to 20 cm. in length by 0.5 to 1 mm. in diameter; is white in color, and resembles *Gordius aquaticus* in general appearance, while the oral papillæ are very similar to those of *Dracunculus medinensis*. Man is the type-host, and the worms are said to occur in the abdominal cavity, vomit, and stools.

(? Filaria) romanorum Verdun, 1907, is said to be an adult threadworm 1 mm. long, found in Roumania by Sarcani, 1888.

Microfilaria powelli Penel, 1905, is a small larval filaria reported for the blood in Bombay; it measures 131μ long, 5.3 μ in diameter, is provided with a sheath, and has a slender truncated tail; periodicity "nocturnal?;" the adult is unknown.

Microfilaria philippinensis Ashburn and Craig, 1906, an embryonic filaria found in the blood of man in the Philippines. Its medical importance is not yet known. Brumpt, 1922, considers it identical with *Wuchereria bancrofti.*

NEMATODES OF THE EYE

Error in interpretation of supposed threadworms in the eye or its immediate surroundings are likely to occur and remnants of arteries, etc., may be mistaken for nematodes unless a microscopic examination of the structure is made. Several of the recorded cases (Quadri, 1857; Fano, 1886 *a;* Schoeler, 1875; Everbusch, 1891) are generally interpreted as based on a confusion of this kind. Other cases, however, are well established, but in some of these the parasites are considered as *species inquirendæ. Trichinella* and *Onchocerca caecutiens* are the most important of these infections; *Loa loa* appears to be less important.

Agamofilaria oculi Siebold, 1839 (*Filaria oculi* Diesing, 1851) is a *species inquirenda*; the worms, varying from 1.72 to 12.6 mm. long, have been reported in 3 cases of cataract.

Filaria conjunctivæ Addario, 1885, 5.5 to 16 cm. long, white to brownish is reported for the eye, ligamentum gastro-lineale, and in cysts on the forearm of man, and in the eye of horses and asses in Europe and India. Life history unknown. *F. apapillocephala* 1892, *F. inermis* 1887, *F. palpebralis* 1867, and *F. peritonei hominis* 1879, are supposed to be identical with this species.

Filaria extraocularis (Skrjabin, 1917), 148 mm. long, vulva 2.4 mm. from mouth, is reported from Caucasus as causing a tumor at the internal angle of the orbit. Its classification as a *Loa* appears to be based upon error.

Filaria circumocularis Ward, 1918 (syn. *F. palpebralis* of Houghton and Stuckley, 1917), reported for the eye of man and dogs in China is interpreted by Leiper as probably identical with *Thelazia callipaeda* Rail. and Henry, 1910, of dogs in Asia. The worms taken from man measure (males) 9 to 14 mm., and (females) 14 to 15 mm. long.

Filaria papillosa Rud., 1802 *a*, of the horse is reported by Macnamara, 1863 *a*, in the eye of man. The diagnosis is *sub judice;* the parasite is interpreted as a synonym of *Setaria equina.*

A conjunctival condition in Australia known as "bungeye" resembles the Habronema granuloma of horses, and on this account is interpreted by Bull, 1922, as probably due to some species of the nematode genus *Habronema*, but the parasite has, apparently, not been observed in man.

NEMATODES OF THE UROGENITAL SYSTEM

Anguillula aceti (Müller, 1783), the vinegar-eel, has been reported several times[1] for the human bladder. It is a very small worm, 1 to 2 mm. long by 24 to 40 μ broad; male with two equal spicules, 38 μ long, and accessory piece; vulva near equator; embryos 222 μ long by 12 μ in

[1] See Stiles and Frankland, 1902 *a*, pp. 35 to 40, Figs. 7 to 13; and Billings and Miller, 1902 *a*.

diameter. The mode of infection has not been demonstrated, but in at least 1 case it was possibly by means of vaginal douches acidulated with vinegar. Symptoms traceable to the parasite were not noticed. The chief importance in connection with this parasite is the possibility of mistaking it for *Microfilaria*.

Leptodera pellio (Schneider, 1866) is recorded (as *Rhabditis genitalis* Scheiber, 1880) as a chance parasite of the vagina and thence in the urine in a case in Hungary reported by Scheiber (1880). The worms measure 0.8 to 1.3 mm. in length; caudal bursa of male with 7 to 10 rays each side; spicules 27 to 33 μ; vulva slightly posterior of equator; eggs 60 by 35 μ. Infection may have taken place by means of poultices made of moist earth. Rhabditiform worms are also reported for the urine by Baginsky (1887 *b*) and Peiper and Westphal (1888). Upon several occasions the writer has found rhabditiform embryos in the urine which he has been unable to identify zoölogically.

Dioctophyme renale[1] (Goeze, 1782), the giant strongyle, or canine kidney-worm, measures 14 to 40 cm. (male) and 20 to 100 cm. (female) long, and is red in color. It is found in the kidneys of dogs and various other animals, and about a dozen authentic cases have been recorded for man. Most of the cases reported for man involve erroneous zoölogical determinations; as ascarids, clots, etc., are mistaken for the giant strongyle. Diagnosis is made by finding the characteristic eggs, 64 by 40 μ, with peculiar mosaic-like shell, in the urine. Treatment is surgical. Vector probably fish, possibly *Idus idus*.

Agamomermis restiformis (Leidy, 1880) is a vivid-red worm, 26 inches long, 1.5 mm. in diameter, which is supposed to have been passed *per urethram* by man in West Virginia. Only 2 cases have been reported. This worm was originally reported as a *Filaria* but reëxamination of the original specimen by the writer has shown that it is an *Agamomermis*.

LEECHES, ACARIASIS, TONGUE WORM INFECTIONS, MYRIAPODA, PARASITIC INSECTS[2]

INFECTION WITH LEECHES (HIRUDINEA)

The blood-suckers resemble earthworms much more closely than they do the intestinal worms. They have a mouth at one end and a sucker at the other. The ordinary medicinal leech belongs to this group. Several species are troublesome to man, more especially in the tropics.

Limnatis nilotica (Savigny, 1820) occurs in North Africa; it is occasionally taken into the mouth with drinking water, and it fastens in the nose, pharynx, œsophagus, or larynx. It has also been found in the vagina and on the conjunctiva. When found, it should be secured with a pair of tweezers, then injected with salt water by means of a hypodermic syringe, and removed as it loosens its hold.

Some blood-suckers, such as the Mexican *Haementeria officinalis*, occasionally cause symptoms of poisoning, when used to draw blood.

[1] Synonym.—*Eustrongylus gigas*.

[2] For literature, apply to United States Bureau of Entomology.

Other leeches in certain tropical localities cause considerable irritation by fastening to the body as persons walk through the grass or brush; *Haemadipsa zeylanica*, a land leech of Ceylon, has an especially bad reputation.

ACARIASIS—INFECTION WITH ACARINES

The acarines include the mites and ticks; they have a segmented or an unsegmented body with 8 legs in the adult stage and 6 legs in the larval stage. Quite a large number of these animals attack man and animals, in some cases acting as the direct cause of disease, in other cases as the transmitter of other parasites.

Treatment.—Sulphur is to the acarines what kerosene is to insects, and not unnaturally it plays a prominent role in the treatment of itch, scab, etc. Of the numerous other acaricides in use, mention should be made especially of balsam of Peru, beta-naphthol, nicotine, phenol, and styrax. The subject is of great economic importance in comparative as well as in human medicine. Several general principles are to be held in mind: (1) The adult parasites are killed more easily than the eggs; accordingly treatment (especially with sulphur) is often directed first against the mites, then a few days are allowed to elapse to permit the eggs to hatch, and a second course of treatment is given before the young mites become mature; this plan presupposes definite data on biology; (2) many acarine infections of man are transient, even self-limited, therefore these types do not call for the vigorous treatment to which scarcoptic scabies is often subjected; (3) some acaricides, if used too freely, produce conditions of the skin which are mistaken for the effect of the parasites; accordingly, over-treatment is unwise; (4) acarines are prone to live under the surface of the skin or scales, and some process of softening the skin or the scales hastens the cure; (5) the lesions produced by acarines are frequently complicated by lesions produced by scratching, and the latter factor is not to be confused with the former; (6) treatment is to be suited to the individual case insofar that a delicate skin (as in children) reacts more intensely to acaricides than does the tougher skin of an adult; (7) treatment is based upon the type of acarine (tick or mite) present; (8) if sarcoptic acariasis is present in a given unit (family; company of soldiers), every member of the unit should be examined for possible infection; (9) in the mite types of acariasis, especially the sarcoptic type, the patient's clothing, bedding, and towels are to be disinfected by heat (80° C.) or by other method.

Ixodiasis—Tick Infection.—The ticks (Ixodoidea) are divided into two families: the *Argasidae*, in which the capitulum ("head") is subterminal in the adults, and the *Ixodidae*, in which the head is terminal in adults. More than 75 species and subspecies, classified in 11 genera, have been reported as attacking man. Most, probably all, of these attack various animals also (mammals, birds, reptiles). Some of them are demonstrated vectors for diseases or parasites in these animals and it is to be expected that the infective ticks transmit the infective agents of these diseases to man, even if the microbic parasite fails to thrive in its new host. Not unnaturally, also, the ticks inoculate into man secretions or other substances in their mouth at time of biting. Not all ticks are known

to transmit disease, and not all tick-bites produce significant results; but in view of the role of ticks in comparative medicine, it should cause no surprise that they are increasing in importance in human medicine, although the exact nature of their effect (as vectors of poisons or of microbes) is not always clear. In general, their effects may be divided into four categories.

1. *Local Lesions.*—Tick bites may produce an almost insignificant to a distinctly troublesome local lesion. Generally, if the tick is removed promptly, and the point of bite washed and dressed, little or no trouble results; as for instance in the vast majority of bites by the Lone-Star tick (*Amblyomma americanum*) and the common dog tick (*Dermacentor variabilis* s. *electus*) of the United States; occasionally, this lesion may swell, ulcerate, become very painful, and continue for some days or even weeks. Exceptionally, ticks may become subdermal. When the tick (as the spinose ear tick, *Otobius megnini*) enters the human ear, the resulting discomfort may become more or less intense, but if a bland oil is poured into the ear, the tick loosens its hold and can be removed.

2. *Tick Paralysis.*—The bites by some ticks are occasionally, though not commonly, followed by a non-fatal or a fatal paralysis which, except for its transient nature, suggests acute poliomyelitis, Thus, in British Columbia, Montana, and Wyoming, a number of cases have been reported, especially in children, exceptionally in adults, five or six days after attachment (on head, neck, back, axilla, calf of leg) of *Dermacentor andersoni.*[1] A sudden and progressive paralysis develops, especially of the legs (sometimes also of the arms, muscles of speech and of swallowing, more rarely of entire body); there may or may not be fever, rapid pulse and respiration, convulsions, stupidity, and other constitutional symptoms, and even (rarely) coma and death. Experimental cases have been produced in lambs and in the dog. Upon removal of the tick and (but sometimes without) administration of a purgative, the patient promptly recovers. The cause of the paralysis (toxic or microbic?) has not been definitely determined. A similar condition is reported in Nature among sheep. In Australia, a tick paralysis in man is reported as result of (and within an hour after) attachment by *Ixodes holocyclus*, which can produce epileptiform attacks in dogs, and paralysis (sometimes fatal) in dogs, cats and sheep. The "Russet tick" (*Ixodes pilosus*) which produces a tick-paralysis in sheep in South Africa, is reported also as a parasite of man. *Haemaphysalis punctata,* of Europe, is reported as causing fatal paralysis in a child.

3. *Tick-bite Fever.*—The term "tick fever" covers many different conditions (Rocky Mountain spotted fever and African relapsing fever of man; various diseases of animals due to "spirochaetes" sensu lato, *Piroplasma*, *Nuttallia*, and *Theileria*) which are not to be confused with "tick-bite fever." Under this latter term reference is made to various febrile conditions which develop in man following bites by certain ticks. Thus in South Africa the bite of the bont-tick (*Amblyomma hebraeum*) some-

[1] This tick, in the Northwest, has been confused with *D. venustus* of Texas. The true *D. venustus* is not known for the North and no authentic case of its occurrence on man is known to the writer.

times results in an elevated temperature, a "dirty tongue," followed by pain and swelling of the femoral glands; the effect on the general health is very depressing and may last several weeks. An immunity appears to result from one attack. If the patients travel, they are very liable to quarantine as plague-suspects. The bite by *Boophilus annulatus decoloratus* may be followed in eight days by a similar condition. *Ornithodoros marocanus* of North Africa is reported as causing a transient fever.

So far as determined, the foregoing (1 to 3) tick-bite conditions appear to be entirely distinct from certain other conditions in which definitely recognized diseases are transmitted (4) by ticks as vectors; but the theoretical possibility is to be borne in mind that "tick-bite fever," "tick paralysis," and local lesions may perhaps be due to the infection with animal diseases into persons in whom the infection does not develop to maturity.

4. *Ticks as Vectors.*—In certain diseases, ticks act either as obligate or as facultative vectors of the infection. Texas fever transmitted to cattle by *Boophilus annulatus* represents the classical example and many other instances might be cited.

In connection with certain diseases of man, some ticks have been definitely demonstrated to be the normal vector, others to be possible (experimental) vectors, still others are under suspicion as vectors. Thus, for the following diseases, the ticks mentioned, may be cited as among the positive or as possible vectors. Relapsing fever of man: *Argas mianensis* (suspected; Persia); *A. persicus* (suspected); *Ornithodoros moubata* (Africa); *O. lahorensis* (suspected; Persia); *O. talaje* (Panama); *O. tholozani* (suspected; Persia); *O. savignyi* (laboratory experiment); *O. turicata* (suspected; Columbia). Rocky Mountain spotted fever: common vector, *Dermacentor andersoni* (often erroneously quoted as *D. venustus*); *D. variabilis*, *D. marginatus*, and *Amblyomma americanum* (experimental). Chaga's disease (*Schizotrypanum cruzi*): *Ornithodoros savignyi* (laboratory experiment). South African tick fever: *Ornithodoros savignyi*.

Treatment.—Ticks not infrequently hang tenaciously to the skin, but if they are covered with oil or vaseline, thus closing their breathing-pores (situated back of the fourth pair of legs), they release their hold more easily. If pulled too roughly, the capitulum ("head") is likely to break off and remain in the skin.

Sarcoptic Acariasis. — Sarcoptic Itch. — Geographical Distribution. — Judging from present records, this infection is almost cosmopolitan.

Zoölogical Distribution.—In the species *Sarcoptes scabiei*, zoölogists recognize a number of different varieties peculiar to different animals. In some cases the mites are intertransmissible between man and animals, and it is not an easy matter to distinguish between the different varieties.

The Parasites.—*Sarcoptes scabiei*, as it occurs on man, is whitish-yellow, round to oval, with transverse rows of small spines and a number of longer bristles. In the female, legs III IV are armed with long setæ; in the male, legs III with setæ, but legs IV have a sucking-disk. The male measures 0.2 to 0.3 by 0.145 to 0.190 mm.; the female is 0.33 to 0.45 by 0.25 to 0.35 mm. The parasites bore irregular galleries, 0.5 mm. to 4 or 5 cm. or more in length, in the epidermis, especially on portions of the body

where the skin is thin and soft, as on the flexor surface of the carpus, between the fingers, in the groins, at knee and elbow, on penis, breast, etc., or at points subject to pressure, as at the waistband. The female is found at the blind end of the gallery; she deposits her eggs (15 to 50 in number) and feces as she progresses. The eggs measure 140 μ and hatch in four to eight days; the parasite becomes mature twenty-eight days after birth. The male dies shortly after copulation. The fecundity is very great. This species is slightly transmissible to horses, dogs, goats, and apes, but not to cats.

Sarcoptes scabiei crustosae Fürstenberg, 1861, is associated with Norwegian itch. There is a difference of opinion as to whether this represents a distinct variety, or the ordinary itch-mite, or the itch of the wolf, which has been transmitted to man. It leads to a more severe condition than the ordinary form of itch.

S. s. equi may be transmitted to man but the infection is short-lived—about three to eight weeks. *S. s. ovis* has been transmitted from sheep to man. *S. s. caprae*, of goats, may be transmitted to man and spread from man to man. *S. s. cameli*, of the camel and dromedary, may cause a severe and persistent itch when transmitted to man. *S. s. aucheniae*, of the llama, also causes a rather serious itch on man. *S. s. suis*, of hogs, sometimes attacks man. *S. s. canis*, of dogs, when transmitted to man, may be temporary or more permanent; the symptoms are similar to those caused by *S. scabiei*. *S. s. vulpis*, *S. s. leonis*, *S. s. wombati*, and *S. minor cati* will all develop on man, that of the cat most easily, but it does not persist.

Source of Infection.—Infection takes place directly from person to person through contact, indirectly through bedclothes, towels, clothes, etc., or in other cases by handling animals.

Frequency.—Itch seems to be decreasing in frequency. It increases during and immediately following a war. It is more especially a disease of the ignorant classes, but may appear in well-to-do persons. In some localities it is exceedingly common, and in others it appears especially among soldiers, sailors, laborers, shoemakers and prisoners. The American Dermatological Association reported it in 4.05 per cent. of about 200,000 skin cases. The writer finds it very common in certain rural districts.

Duration.—As successive generations develop in the skin, the untreated condition is not limited by the longevity of a single generation, but is potentially indefinite. It may last for years or even decades; it may disappear temporarily but not completely. Spontaneous cure is said to be unknown.

Symptoms.—The penetration of the mites (namely, in forming the galleries or burrows) causes an intense itching which leads to scratching, and increases under influence of heat, exercise, and especially when the patient is in bed. Various eruptions appear; papules, vesicles, and pustules form. The galleries may be white, but, because of the presence of eggs and acarine excrement, they usually become grayish to blackish; these galleries are not equally distinct in all cases. Vesicles are usually present and vary in number; they appear early in the same localities

as the galleries; they are transparent at the summit, rose-colored at the base, and contain a limpid fluid; in time they dry and form a small thin, yellowish crust; but if scratched they may become pustular. The papules appear at various places on the hands, arms, etc., and are the seat of intense itching; they rapidly increase in number, but rarely attack the face. It is stated that in 99 per cent. of cases in men lesions are found on the penis, and in 99 per cent. of cases in women, on the breast, around the nipple. The action of the parasites is both mechanical, in tunnelling through the skin, and chemical. Additional injury is incurred by scratching; sleep may be seriously disturbed by the itching; fatal cases seem to be unknown.

Norwegian itch (scabies crustosa) is reported for Norway, Germany, Austria, France, Denmark, Russia, Turkey, and the United States, but is rare. It is characterized by the development of adhesive yellowish or grayish crusts, in which numerous mites are found in irregular galleries. On the palms, soles, and knees, these epidermic callosities develop 1 to 6 mm.—even 12 to 30 mm.—thickness; they may also form on the head; the hair falls; the nails thicken and become like claws, reaching 20 mm. in thickness in some cases. Cases of Norwegian itch are of long standing, three to sixteen years, and in very slovenly people. Treatment must be prolonged and energetic.

Diagnosis.—The affection is recognized from the presence of the galleries with the female at the end. These become more distinct if the part is washed. In case of doubt the parasite or its eggs may be recognized microscopically.

Treatment.—It is difficult to mention a disease for which as many treatments exist as for sarcoptic itch. Especially in pronounced cases, two essential points are to be considered: (1) To prepare the skin so that an acaricide can act; (2) to apply the acaricide. Various modifications are adopted; the following may be taken as a radical guide, to be modified according to facilities and according to the delicacy of the skin or condition of the patient:

1. The patient, stripped naked, is energetically rubbed all over (sometimes including the head) with a wash-cloth or a brush for twenty minutes with green soap and warm water. 2. He is then placed in a warm bath for thirty minutes, while the rubbing is continued. 3. The parasiticide is next rubbed in for twenty minutes and is allowed to remain on the body four or five hours; in the meantime the patient's clothes are sterilized, to kill eggs or mites attached to them. 4. A final bath is taken to remove the parasiticide.

In treating acariasis (particularly the psoroptic form) in domesticated animals, it is common experience that whatever acaricide is used, much better results are obtained if it is applied as hot as can be conveniently borne. A striking feature of the literature on the treatment of saroptic acariasis in man is the paucity of reliable biological data cited and upon which the treatment is predicated. Surely, the daily or twice-daily repetition of inunctions is based upon an idea of thoroughness rather than upon exact biological knowledge, and it is difficult to escape the (possibly erroneous?) impression that treatment would be easier, more uniform, and

more efficient, if a thorough academic restudy of the biology of the parasite were made. Theory, supported by standard practices in psoroptic scab, indicates that the treatment of sarcoptic itch should consist either of a single application which would kill both the mites and their eggs, or of two or three applications timed with an interval slightly shorter than the time required for the newly hatched mites to reach maturity.

Of the scores of formulæ and routines advocated by various authors, only a few will be cited here—but all with the reservation that however satisfactory they have proved in practice, their advocates have not presented evidence of the desirable biological control on basis of which they have been published. In other words, they are more or less empiric, despite their success, and some of them seem unnecessarily complicated.

1. Probably the most simple, though somewhat prolonged, technique is the dusting of powdered sulphur on the body and in the bed (between the sheets) every second or third night. Cures are reported in seven to ten days. Obviously this technique depends upon permitting the eggs to hatch and then killing the mites by direct or indirect contact with the sulphur.

2. Fumigation with sulphur dates back many years and has recently again come to the fore. It presents the advantage of the possibility of a single and prompt treatment, but theoretically it is not dependable. The patient is placed in a cabinet, head out, carefully watched, and promptly removed if ill-effects are noticed. Sulphur is burned in the cabinet; the fumes kill the mites and probably many of the eggs.

3. The sulphur bath corresponds more or less to the lime and sulphur treatment of psoroptic scab. Sulphurated potassa 3 to 6 ounces (96 to 192 gm.) to 30 gallons of warm water. Patient bathes fifteen to thirty minutes; rubs thoroughly with wash-cloth or brush, according to condition of the skin.

4. Hot bath half an hour, scrub body with soft soap; patient then rubs in sulphur ointment, 24 ounces (700 grams) (4 ounces minimum to cover body once), puts on old sleeping suit, gloves, and socks, and remains in bed until time for bath next day. Treat not more than three consecutive days.

5. A.—For patients with a delicate skin: Night and morning for two to three days, hot bath, soap (green soap if skin is not oversensitive). Then rub in either of the following ointments: (*a*) Sublimed sulphur and balsam of Peru (each 2 to 6 drams (8 to 24 gm.)) and benzoinated lard and petrolatum (a sufficient quantity of equal parts of each to make 4 ounces (128 gm.)). Or (*b*) sublimed sulphur 2 to 6 drams (8 to 24 gm.), balsam of Peru 4 drams (16 gm.), beta-naphthol 1 to 2 drams (4 to 8 gm.), and benzoinated lard and petrolatum (equal parts of each to make 4 ounces (128 gm.).

B.—A more radical routine, for tough skin: Hot bath, with green soap. Then sublimed sulphur 2 parts, potassium carbonate 1 part, and lard, 12 parts.

7. "Danish" (single application) treatment: An ordinary cleansing bath; dry thoroughly, rub ointment on entire body except head, air-dry fifteen minutes, then go to bed; about twenty-four hours later, patient bathes,

puts on clean underwear, and is discharged (but followed up). The rather complicated ointment (made in large amounts) must be properly prepared or dermatitis may develop: (*a*) Mix 1 kg. sublimed sulphur with 2 kg. of 50 per cent. solution of potassium hydroxide (as free from water as possible); heat gently until reaction ceases and solution becomes clear; sulphur must be slightly in excess. (*b*) Mix 225 gm. petrolatum with 225 gm. wool fat, without heat. (*c*) Mix 375 gm. of *a* with *b*. (*d*) Mix 40 gm. of 20 per cent. sodium hydroxide with 28 gm. zinc sulphate, shake thoroughly until reaction ceases, pour on filter paper, wash thoroughly add wash precipitate to *c*. (*e*) Add liquid petrolatum to make total of 1000 grams. (*f*) Add 5 gm. oil of bitter almond.

Obviously this complicated ointment seeks (1) to penetrate the upper layers of the skin, (2) to kill the mites, and (3) to destroy the eggshells, and insofar it corresponds to both the lime and sulphur and the phenol treatments for psoroptic scab.

8. Beta-naphthol 15 parts, prepared chalk 10 parts, soft soap 50 parts and lard 100 parts. (Kaposi.)

9. Bathe. Then rub with balsam of Peru 3 parts and glycerin 1 part. Allow ointment to remain on body one week, then take hot bath. Albuminuria sometimes results. (Sequeira, 1919; *et al.*)

10. Kaposi (1895) considers baths and friction unnecessary in moderately severe cases and, if eczema is present, even harmful. He suggests as ointment (*a*) Styrax 5, petrolatum 15, olive oil 15, balsam of Peru 10, and spirit of potash soap 20: or (*b*) sublimed sulphur 15, vaselin 25, lanolin 25, oil of lavender 5 drops, peppermint 5 drops, and orange flowers 5 drops.

11. Either sulphur, or styrax, or (preferably) balsam of Peru, 10 per cent. strength in an ointment base, preferably cold cream. Rub in 1 ounce, 4 successive nights; long, hot, soap bath precedes first and fourth inunctions. (Highman, 1921).

12. Styrax 1 ounce and lard 2 ounces. Less irritating than sulphur. (Sequeira, 1919.)

In light infections, the lesions heal after the mites are killed, but in severe cases the patient may require additional dermatologic attention.

Demodectic Acariasis.—Infection with hair-follicle mites.

Geographical Distribution.—Probably more or less cosmopolitan.

Zoölogical Distribution.—The hair-follicle mite, *Demodex folliculorum*, is reported not only for man but also for quite a number of animals, as dogs, cats, horses, cattle, hogs, etc. The forms which attack animals are usually considered specifically identical with that which attacks man, but as representing distinct varieties. There is some doubt at present regarding the intertransference of these varieties between animals and man; if such infection does occur it seems to be rare. The infection in dogs is the classical example of the disease; it is very difficult to cure, and quite fatal. In cattle the infection is of considerable economic importance from its effect upon the hides.

The Parasite.— *Demodex folliculorum*,[1] as found in man, is an elongate, worm-like mite, 300 to 380 μ long by 40 to 45 μ broad, with rather short,

[1] Synonyms.—*Acarus folliculorum* Simon, 1842; *D. folliculorum hominis*.

broad rostrum, and 4 pairs of short legs. It is very common in the sebaceous glands of the face, alæ of nose, lips, cheeks, forehead, Meibomian glands, and is also found in the cerumen, venter, dorsum, hair follicles of the chest, and at the root of the pubic hairs. In healthy glands only a few (1 or 2 specimens) are found, but the number may increase to 15 or 20 or even many more; usually the head is toward the bottom of the follicle. This parasite multiplies very slowly, passing through the stages of egg, hexapod larva, octopod nymph, second nymph, and adult. It may live six or more days after the death of the host.

Source of Infection.—So far as known, and judging from analogy, infection may be direct or indirect from person to person.

Frequency.—Guiart (1902 *b*) has found this parasite in all cases in which he has looked for it; Gruby found it in 40 out of 60 persons examined. It is apparently much more common in adults than among children.

Duration.—The longevity of the individual parasite is not established so far as known to the writer, but judging from the life-cycle of the parasite a case of infection is potentially indefinite.

Symptoms.—That the effect of the hair-follicle mite has been both overestimated and underestimated is probably quite certain. The vast majority of cases pass unnoticed, but 1 case has been seen by the writer (in man) of nodular formation as large as a pea, caused by these parasites. The relation of the mite to acne is *sub judice;* that they may be one cause of acne seems, *a priori,* probable. It has been reported as concurrent with cancer, but they are so common that this concurrence is not strange.

Treatment.—Several authors intimate that these parasites are easily killed, but in view of the difficulty experienced in treating the affection in dogs, etc., a question regarding the correctness of the interpretation in the cases in man, naturally and legitimately arises.

OTHER FORMS OF ACARIASIS

Of the numerous other mites reported for man, probably the most important for this country are:

The harvest mites (*Leptus americanus* and *L. irritans* Riley; *L. autumnalis* Shaw, 1790, is a European species), also known as the "red bug" or "harvest bug," or "chigger" or "jugger." These are hexapod larvæ of mites; according to Ewing, the North American jiggers represent the young stage of *Trombicula tlalzahuatl,* while the European jiggers represent at least three different species. They attack man in the fields in summer and burrow into the skin, causing a very irritating sensation, and even a considerable amount of suffering, increased by scratching. Occasionally children scratch off considerable areas of skin, especially on their legs. The symptoms disappear after a few days.

Treatment.—A warm bath within a few hours after exposure; rub lesion with carbolized vaseline, sulphur ointment, or corrosive sublimate (2 to 1000); extraction of the parasite with a fine needle.

Pediculoides ventricosus is a minute mite that attacks persons working with infested wheat or straw, or sleeping on infested straw mattresses, and causes a condition known as straw-itch, straw-mattress itch, or der-

matitis schambergi. This eruption may occur in single cases or in epidemic form, not only in wheat areas, but in localities to which the wheat, straw, or straw-mattresses are shipped. The differential diagnosis (from chiggers, scabies, and common hives) is easily made by finding the very elongate mite which has but a feeble attachment to the skin.

Within twelve to sixteen hours after exposure the first and invariable symptom, itching, appears; in severe cases, and especially when the cause is not suspected or recognized and the exposure is continued night after night by sleeping on an infested straw mattress, for example, the itching may become almost intolerable. The eruption appears simultaneously with the itching, and characteristically consists of wheals surmounted by a vesicle. The latter, as a rule, does not exceed a pinhead in size, but it may become as large as a lentil seed or pea. Its contents very rapidly become turbid, and the vesicle is converted in a few hours into a pustule. Instead of frank wheals there may be erythemato- or papulo-urticarial lesions, which are irregularly circular or oval in outline, from a lentil to a finger nail in size, and usually of a warm rose tint. The pinkish-white anemic area of ordinary "hives" is rare. The eruption is most abundant on the trunk, slight on the face and extremities, and practically absent from the feet and the hands. Even when experimentally exposed to attack, the limbs, for some reason, largely or altogether escape. The onset in severe cases may be marked by chilliness, nausea, and vomiting, followed for a few days by a slight elevation of temperature with the appearance of albumin in the urine. In the less severe types there may be only some diminution of appetite, with malaise, or a constitutional reaction may be altogether absent.

P. ventricosus does not bore into the skin. Its attachment to the surface being feeble, it is readily brushed off by the friction of the clothes; local antiparasitic treatment is therefore hardly necessary. If desired, however, a mild sulphur ointment will answer this purpose. Antipruritic treatment is always called for; warm, mildly alkaline baths or some simple soothing ointment, such as zinc oxide, will be found to fulfil this indication. Of course, contact with the suspected straw or grain must be discontinued. The clothes and body linen must be changed, but as the mite cannot survive more than a day without food, airing them for a day or so will be sufficient to free them from danger.

The kedani mite, known as *Trombicula* (also *Leptotrombidium*, *Microtrombium*, *Trombidium*, and *Leptus*) *akamuski*, is a Japanese acarine which is accepted as the vector of "river fever;" the organism associated with the disease is supposed by Takana (1889) to enter through the puncture in the skin made by the mite.

Tydeus molestus was probably imported into Belgium with Peruvian guano. It attacks man, sometimes amounting to a serious torment.

Chicken mites (*Dermanyssus gallinae*), and a closely allied species (*D. hirundinis*) from swallows, may attack man, causing a cutaneous eruption with considerable itching.

Holothyrus coccinella attacks birds, especially ducks and geese, in Mauritius; it attacks man, causing a cutaneous swelling with a burning sensation; it is said to enter the mouth of children.

Various mites are accidentally swallowed in food (cheese, etc.) or water and are found in the feces. Among the acarines reported for the feces may be mentioned *Glyciphagus domesticus* and *G. prunorum;* the former causes a condition known as "grocers' itch."

Tyroglyphus farinae attacks men handling grain; this and *T. siro* are said to cause the cutaneous (not the nervous) type of vanillismus.

Histiogaster spermaticus Trouessart, 1900, is a mite reported as having been found in a cyst in the testicles; it may possibly have gained access by being introduced into the urethra in catheterizing.

Necrophagus sanguinarius Miyake and Scriba, 1893, was found dead in the urine in a Japanese case of fibrinuria with hematuria and chyluria; it was supposed to have come from the kidneys, but there is room for grave doubt concerning this point.

Of the numerous other mites reported for man, mention is to be made of the following: *Acaropsis mericourti* (in ear); *Carpoglyphus alienus* (urine); *Cheyletus eruditus* (ear); *Chorioptes bovis* (skin); *Cnemidocoptes mutans* (skin); *Cytoleichus hominis* (omentum); *Histiogaster entomophagus* (skin); *Laelaps stabularis* (skin); *Leiognathus morsitans* (skin); *L. sylviarum* (intense pruritus); *Liponyssus americanus* (skin); *L. bacoti; L. bursa; Metatrombidium poriceps* (summer chigger, Europe); *Microtrombidium batatas; M. brumpti; M. meridionale, M. pusillum, M. wichmanni* (skin); *Psoroptes equi* (skin); *Rhizoglyphus parasiticus* (skin); *Schöngastia vandersandei* (shrub itch); *Tarsonemus floricolus* (urine); *T. hominis* (ovarian tumor); *T. intectus, T. uncinatus; Tetranychus molestissimus, T. telarius; Trombidium striaticeps* (skin, Europe); *Typhlothrombium deliense* (pseudotyphus); *Tyroglyphys casei* (urine), *T. longior* (urine, intestine).

POROCEPHALIASIS OR TONGUE-WORM INFECTION

Tongue worms (*Linguatulidae*) are degenerate arthropods. At least four (? five) species occur in man. Usually the diagnosis is made at autopsy. In the majority of instances the presence of the parasites has not explained the medical history of the case, but in a few heavy fatal infestations there have been pneumonia and peritonitis which were in harmony with the infections. These infections do not belong to the normal diseases of man, since man is not a normal host in the life cycle of the parasites.

Linguatula serrata Frölich, 1789, measures 18 to 45 mm. (male) long by 3 to 4 mm. broad, and 8 to 13 cm. (female) long by 8 to 10 mm. broad. The adult stage inhabits the nasal passages of canines, while the larvæ, which measure only 4.5 to 5.5 mm. long, are encysted in the liver, lungs, etc., of rabbits, cattle, sheep, and various other animals. Both the larval and the adult stages are recorded for man, especially in Europe. The larva has been found also in American cattle and rabbits. The writer has seen cases of supposed intestinal tuberculosis in cattle which were due to this infection. Pseudorabies in the dog may result from infection with the adult stage. In cases of nasal infection with gravid females, the diagnosis may be made by finding the four-legged embryo, enclosed

in its egg-shell, in the nasal discharge; diagnosis of infection by the encysted larva has been made postmortem in a number of cases, but no symptomatology has been described.

The larva of *Armillifer armillatus* (Wyman, 1847) is reported as encysted in various organs of man in Africa. The adult lives in the lungs of the Royal Python and of other snakes. *Pentastomum constrictum* (also reported for man) is viewed by Sambon as identical with this species. The larval parasite is encysted in various organs.

The larva of *Armillifer moniliformis* (Diesing, 1836) is reported for man in Africa, Asia, and the Philippines, but Sambon views the African cases as *A. armillatus*. The adult is found in the lungs of various snakes (*Python reticulatus* and others). In a case reported for Africa by Broden and Rodhain (1909) the infection was generalized; Seiffert (1910) found 17 cases of infection in 218 autopsies in Kamarun. Raebiger (1910) reports an African case of porocephaliasis in which the infection extended to the brain. In both *armillatus* and *moniliformis* infections, man is only an accidental host; the larval forms are found also in various monkeys, rodents, etc. For summary of cases in man see Sambon, 1909 and 1910, *Jour. Trop. Med. and Hyg.*

Porocephalus subulifer is cited by Sambon as a parasite of man, and a case reported by Osler for Toronto is now interpreted as possibly due to *Porocephalus crotali.*

MYRIAPODA

The myriapods are not true parasites in man, but occasionally, they are found as accidental parasites in the nose or intestine. Blanchard (1898 *c*) collected 35 such cases.

PARASITIC INSECTS

Adult insects have 6 legs, and, usually, 2 or 4 wings. The larvæ are more or less worm-like, and are known as "grubs," "bots," etc. Both the larval and the adult stages may be parasitic. They are of more importance in medicine as transmitters of disease (mosquitoes and malaria, yellow fever, and filariasis; flies and sleeping sickness; fleas and plague; lice and typhus) than they are as parasites (fleas, lice, grubs, etc.), and we may lay down the *general* rules that diseases (such as malaria, filariasis) which are biologically dependent upon insects and other arthropods for their distribution, are caused by animal parasites, while those (such as typhoid) which may be mechanically disseminated by arthropods, but are not dependent upon them, are usually caused by plant parasites.

Burrowing Fleas: Jigger Flea, Chigger or Chigoe.— Geographical Distribution.—This is a tropical and subtropical parasite of American origin; it has been introduced into Africa and adjacent islands, where it has spread rapidly; it is reported for Persia, India, and China.

Zoölogical Distribution.—This parasite attacks not only man, but also horses, cattle, swine, and dogs. It is said to attack chickens and certain other birds; but, as a distinct species (*Echidnophaga gallinacea*) is found on chickens and also reported as attacking man, it might be well to

reëxamine this infection to see whether a confusion in determination has occurred.

The Parasite.—*Tunga penetrans*[1] (Linnaeus, 1758) is about 1 to 1.2 mm. long; when young, the female resembles other fleas, but, after mating, it burrows into the skin and swells into a body resembling a beet in appearance. The female remains in the skin about three weeks. The males do not burrow. The eggs hatch out on the ground and the larvæ undergo a resting stage.

Frequency.—In some localities this infection is very common. Manson stated that it causes a large amount of invalidism among the coolies in East Africa. There may be only one or two parasites present, or the fleas may be so numerous and thickly set as to give the infected part a honey-combed appearance.

Symptoms.—The fertilized female burrows into the skin, especially on the feet, but also on other portions of the body, forming small, pea-like, elevated swellings; the caudal end of the flea may be seen at the opening of the burrow. The parasite causes considerable irritation; pus forms around it; the skin may ulcerate, leaving a sore.

Diagnosis.—The diagnosis is not difficult. The pea-like swellings on the feet, especially under the nails and between the toes, are in themselves suspicious, and a closer examination reveals the parasite.

Treatment.—The entire parasite should be pried out with a sharp knife or similar instrument, when possible without breaking. Application of chloroform, or mercurial ointment may first be used to kill the flea. The wound is thoroughly cleansed and dressed.

Prevention.—The wearing of shoes in the infected districts will greatly reduce the chances for infection.

Jumping Fleas.—*Pulex and Ctenocephalus.*—**Geographical Distribution.**—Cosmopolitan.

Zoölogical Distribution.—Fleas are common on numerous different species of animals, and some of the species are intertransmissible between man and their normal hosts.

The Parasites.—There are two fleas in particular which attack man: *Pulex irritans* (Linnaeus, 1758), known as the "house flea" or "common flea," is more common in Europe than in the United States.

Ctenocephalus canis and *C. felis* the ordinary "cat and dog fleas," seem to be more common in the United States than *P. irritans;* they differ from *P. irritans* in the presence of a comb-like structure on the first thoracic segment. The flea-eggs develop in cracks in the floor and other suitable places. In the case of *C. canis* the egg stage lasts one day, the first larva, three to seven days, second larva, three or four days. They commence spinning from seven to fourteen days after hatching, and the imago appears five days later; thus an entire generation may develop in a little more than a fortnight.

Medical Importance.—Adult fleas may: (*a*) attack man as ectoparasites; (*b*) act as intermediate host for certain worms (*Dipylidium caninum, Hymenolepis diminuta*), threadworms (*Dirofilaria immitis*), and they have

[1] Synonyms.—*Pulex penetrans* Linnaeus, 1758; *Sarcopsylla penetrans* Westwood, 1840.

been suspected in the transmission of protozoa (*Leishmania*); (*c*) act (especially *Xenopsylla cheopis* of rats) as disseminators of plague. Flea-larvæ are also reported as pseudoparasites in man.

Prevention.—Many methods are suggested to protect against the attacks of fleas, as, for instance, the use of essential oils; but the reports from their use are not very encouraging. It is better to clear the fleas out of the house by a vacuum cleaner, fumigation with sulphur, by sprinkling pyrethrum powder or naphthalene or by washing the floor with benzine, kerosene, or hot soap-suds.

Pediculosis: Lousiness.—There are three species of lice which attack man: namely, the head-louse, the body-louse, and the pubic-louse.

Geographical Distribution.—Cosmopolitan.

Zoölogical Distribution. The three lice typical for man do not normally live on other animals; occasionally lice from various animals attack man, but remain on him only a short time.

The Parasites.—The head-louse (*Pediculus humanus*[1] Linnaeus, 1758) lives among the fine hairs of the head; the female lays 50 to 60 eggs or "nits" within six days; these white "nits" are attached to the hair, especially back of the ears; they hatch on the sixth day; the young become mature in seventeen to twenty days.

Pediculus corporis[2] de Geer, 1778, the body-louse, secretes itself in the folds of clothing, but draws its food from the body; it lays 70 to 80 (or, according to other observations, 8 to 10 per day for about thirty days) eggs in the folds of the clothing; these hatch in three to four (or in eight or nine days at 87° F.) days and mature in twelve to eighteen days. The adult louse lives about thirty-four to forty days.

The pubic-louse, or crab-louse, *Phthirus pubis*[3] (Linnaeus, 1758) is much more common on men than on women; it is found chiefly on the pubes, occasionally on the eyelashes, and is reported also for the head. It lays 10 to 28 eggs, about 2 per day, which hatch in six to eight days and become mature in fifteen days. This adult lives about fourteen days.

Source of Infection.—Lice may pass directly from one person to another or may be carried by flies. Beds are also sources of infection.

Symptoms.—Head-lice may cause an irritation accompanied by an eczema or pustular dermatitis. The discharge, mixed with excoriations due to scratching, mats the hair together; scabs and crusts form; if allowed to run, a regular carapace may form, called *trichoma*, and the head exudes a fetid odor. Various low plants and mites may grow in the trichoma, the entire structure being known as the *plica polonica*.

Body-lice cause rose elevations, analogous to urticaria, and papules which become excoriated at the summit and covered with brownish crust; itching and scratching result, and white scars are found, surrounded by brownish pigment; the skin may become thickened and takes on a bronzed tinge, presenting a melanoderma which is one of the chief attributes of vagabonds' disease.

Pubic-lice cause an irritating pruritus, especially at night; a dry prurigo,

[1] Synonyms.—*P. capitis* de Geer, 1778; *P. cervicalis* Latreille, 1803.
[2] Synonyms.—*P. vestimenti* Nitzsch, 1818; *P. tabescentium* Alt, 1824.
[3] Synonyms.—*Ped. pubis; P. inguinalis; Phthirius inguinalis.*

represented by small rose or reddish papules; and in some cases in the subumbilical region, on the flanks and internal surface of the thigh, bluish-gray temporary spots, 7 to 8 mm. in diameter, not painful and not paling much on pressure.

Both head-lice and body-lice carry European relapsing fever and typhus, and the body-louse transmits trench and quintana fever; the pubic-louse is suspected as a carrier of relapsing fever.

Treatment.—If feasible, as in male patients, it is well to cut the hair, although this is not at all necessary. Saturation of the head with kerosene emulsion will kill the lice, but carbolic washes are more severe on the eggs ("nits"). Washing with tincture of *Cocculus indicus* is advised by some authors, its advantage being the absence of odor. The same measures may be used for the pubic-louse; or mercurial ointment may be applied. In treating the body-louse, it is the clothes more than the body which need radical treatment. The entire clothing should be baked or boiled. The itching may be allayed by warm baths, sodium bicarbonate being added to the water.

Bed-bugs.—Geographical Distribution.—Cosmopolitan.

Zoölogical Distribution.—The popular view that bed-bugs are carried by swallows and bats is erroneous; generically identical but specifically distinct parasites infest these animals.

The Parasite.—There are two bed-bugs which infest dwellings in this country. The "common bed-bug," *Cimex lectularius* Linnaeus, 1758, does not require description. It is a very intelligent animal, which secretes itself in crevices, in cracks, in draperies, and around the buttons of mattresses during the day, seeking its food at night. It lays eggs from which the larval stage issues; in its development it sheds its skin, and it feeds once between every two moultings, then once again after the last moult before it lays its eggs.

The Mexican bed-bug, or blood-sucking cone-nosed bug (*Conorhinus sanguisuga*), is spreading from Mexico toward the North. The adult possesses wings. This is normally a predaceous insect rather than a parasite, and it feeds upon the bed-bug. Having tasted human blood from this source, it is now acquiring the habit of attacking man.

Source of Infection.—Bed-bugs wander from house to house, but they are usually spread through the moving of old bedding, or in clothes. The laundry is a common source of importation, especially in localities like Washington, where negroes take the laundry to their homes.

Symptoms.—The writer is convinced that the common bed-bug may occasionally be of greater medical importance than is usually attached to it. He knows, for instance, of one case where a young man underwent treatment for neurasthenia; all symptoms promptly disappeared, however, immediately following a thorough fumigation of his rooms, where nearly a pint of bed-bugs was collected. The effect of bed-bugs upon delicate or young children, in loss of sleep, is occasionally a matter not to be entirely ignored; this is a point of importance in many families in certain factory and rural districts, but it is frequently overlooked.

Treatment.—This consists in removing the cause. Above all methods, the writer favors thorough fumigation of the house with powdered

sulphur (2 to 3 pounds to 1000 cubic feet of space). For practical reasons, in order not to attract attention, it is best to start the fumigation in the evening after dark. The sulphur is placed in wash-basins, old kettles, etc., and these dishes are set on bricks in larger basins or tubs containing water enough to come close to the top of the dish containing the sulphur; a small well is made in the sulphur with the finger and a small amount of alcohol poured in; the alcohol is then set on fire and the sulphur allowed to burn out. All windows should be tightly shut, and the room should remain closed for twelve to twenty-four hours. Metal ornaments, clocks, valuable tapestries, etc., should be removed before fumigating.

The treatment with hydrocyanic-acid gas is too dangerous for general adoption, especially among the more ignorant classes, as the fumigation is usually carried out by women in the family, who in their haste to leave the room when the gas is started may trip on their dresses; fatal accidents are reported. The sulphur fumigation does not present this danger. The ordinary methods of washing with kerosene, gasoline, etc., are good so far as they go, but are less reliable than thorough fumigation with sulphur. A plumber's torch can be used to advantage on iron beds; a saturated solution of corrosive sublimate in water may be used in the cracks of wooden beds, floors, etc.

Myiasis.—Dipterous Infection.—The term "myiasis" is used to denote an infection with the larval ("grub") stage of dipterous insects. Various authors distinguish a *Myiasis externa* and *interna*, *M. intestinalis* and *dermatosa*, or *M. oestrosa* and *muscida*, the first four terms being based upon the position of the parasites, the last two on the zoölogical classification. For American physicians, the most important is the—

Screw-worm.—*Compsomyia macellaria* is a fly which deposits its eggs in wounds. It may also oviposit in the nostrils of persons (particularly those with offensive catarrh) when sleeping out of doors. The larva, known as the "screw-worm," issues within a few hours, and burrows into the tissues; it feeds for five or seven days, then exits to pupate. Accordingly, in case of infection the larvæ continue their active injury for five to seven days. Infection with this larva may be serious, and even (21 deaths in 31 cases, Maillard) fatal. An effort should be made to kill the larvæ by douching with a 20 per cent. solution of chloroform in sweet milk; some of the parasites may be removed with simple salt water, or with forceps. Various larval insects are also found in fresh wounds, and have been especially troublesome in time of war.

A discussion of the numerous fly larvæ reported for man would carry us far beyond the limits of this article. Descriptions of the parasites and accounts of symptoms are to be found in various works on parasitology and medical entomology. Suffice it here to say that creeping-disease or larva migrans, often assumed to be due to a fly larva, may be due to nematodes also, and probably to several different insects.

Scoleciasis.—Scoleciasis is a term used to designate accidental infection with coleopterous larvæ. *Necrobia* sp. has been reported for the eye.

Miscellaneous.—The reported cases of snakes, frogs, earthworms, etc., as parasites are instances of spurious parasitism.

PART V

DISEASES DUE TO PHYSICAL AGENTS

CHAPTER XX

HEAT STROKE. INCREASED ATMOSPHERIC PRESSURE. DECREASED ATMOSPHERIC PRESSURE. THE UNTOWARD EFFECTS OF ELECTRICITY

By ELMER H. FUNK, M.D.

HEAT STROKE

Synonyms.—Heat Exhaustion, Heat Hyperpyrexia, Heat Prostration, Thermic Fever, Sunstroke, Sun Traumatism, Insolation, Siriasis, Coup de Soleil, Thermoplegia.

Definition.—A morbid condition caused by exposure to excessive heat and characterized clinically either by evidences of collapse and subnormal temperature (heat exhaustion) or a rapidly rising temperature with dry skin and nervous disturbances (heat hyperpyrexia), or by painful muscle spasms (heat cramps). The term, sunstroke or sun traumatism, has been restricted by some observers to those cases which were thought to result exclusively from exposure to the direct rays of the sun. The separation of this group is not generally accepted. A forcible expression of opinion in this regard is that of Ogilvie, "if a victim was bowled over in the sun, the case is sunstroke; if he was in the shade, it is heat stroke, the symptoms being identical."

Physiological Considerations.—The remarkably constant temperature of the body under varying conditions is dependent upon a complex heat regulating mechanism under the control of the central nervous system by which heat production and heat dissipation are kept in equilibrium. The ultimate source of heat is the potential energy of the ingested foods. Every bodily function, especially muscular contraction, is accompanied by the evolution of heat. Heat liberation results from the warming of food, drink, and the inspired air, the evaporation of water from the skin and lungs, and from radiation and conduction of the skin. The variable factors of heat production and dissipation are coördinated in health. Disease frequently upsets the heat-regulating mechanism. Excessive external temperatures may likewise give rise to thermo-regulatory disturbances. Under ordinary conditions if the external temperature is

high, there occurs an increased activity of the circulation and the respiration, a dilatation of the superficial bloodvessels, and an increased activity of the sweat glands. These favor heat liberation. If the atmosphere is in motion and possesses a low relative humidity rapid evaporation from the skin favors lowering of the bodily temperature. If, however, the air is not in motion and possesses a high relative humidity, evaporation is reduced.

The physiological effects of high temperatures and humidities with and without air movements were recently studied in hot and deep metal mines by Sayers and Harrington.[1] Resting in a saturated air at 95° F. with no air movement produced an increase in body temperature and pulse-rate, an increase in pulmonary ventilation, profuse sweating, and dizziness on movement. These effects, apart from the profuse sweating, were slight or absent if air was kept in motion. At 98.5° F. symptoms were produced even in the presence of moving air. At 100° F. resting in a saturated air produced, without and with air movement, a marked rise in body temperature (102.3° F.); a marked rise in pulse-rate (varying from 152 to 175), profuse sweating, and the early appearance of dizziness and weakness. These studies indicated that the untoward effects upon man of almost saturated air with temperatures between 90° and 98° F. are much less when air is moving than when it is still, but in higher temperatures, 98.5° to 100° F. no beneficial effect was obtained by moving air, even at high velocities; and there was apparently some disadvantage.

In many parts of the world man is exposed to temperatures as high as 110 to 120° F.; and in certain occupations, such as stokers on steamers, the temperature may reach 150° F. There is good evidence which cannot be reviewed here that apart from temperature effects *per se*, exposure to excessive heat may be associated with the accumulation of toxic products of protein ketabolism giving rise to an auto-intoxication.

Etiology.—High atmospheric temperatures, high relative humidity, and lack of evaporation from the skin may be considered as direct etiological factors in both heat hyperpyrexia and heat exhaustion. These are common in the tropics and in other parts of the world during hot weather, as well as in certain occupations. In the tropics new-comers are more liable to heat effects than natives or residents who have become acclimated. At Busra in Mesopotamia, one of the hottest stations to which British troops are sent (the temperature during July and August may reach 120° F.), there were 24 cases of heat hyperpyrexia per 1000 British in July, 1921.

In Chicago in 1916 during an unusually hot July there were 158 cases admitted to Cook County Hospital with 70 deaths (Gauss and Meyer). In the U. S. Registration Area for 1921, 946 fatalities from excessive heat were recorded. There were twice as many deaths among men as women. Although no age was exempt, two-thirds occurred either before two years or after fifty years of age, exemplifying the lessened tolerance to heat at the extremes of life. Certain occupations, such as stokers on steamers, workers in steel mills, hot mines, sugar refineries, etc., are exposed to

[1] *Public Health Reports*, 1923, **38**, No. 29, 1616.

high temperatures. There are certain important predisposing factors. According to Hearne, there is a great variation in the individual capacity for sweating which may be a determining factor in heat stroke. In others continuous exposure to heat causes exhaustion of the sweat glands with subsequent reduction in heat dissipation and the accumulation of toxic products in the body. Alcoholism and debility from any cause lessen the adaptability of the body to high temperature. Dietary indiscretions, insufficient fluid intake, unsuitable clothing, and overcrowding are predisposing factors. Muscular exertion is a very potent factor, since most of the cases occur in those who have been overworked. The absence of heat stroke on oil burning ships in which the fire rooms are of a higher temperature than on coal burning ships, is attributed by Fiske to less fatiguing work and less crowding.

Increasing importance is being attached to an auto-intoxication, either as the result of excessive or perverted protein ketabolism or diminished excretion of toxic products through the skin and other channels, as explaining some of the features of heat stroke.

In a certain group of cases (sunstroke) direct exposure to the rays of the sun has been considered the etiological factor. It has not been shown, however, that any rays other than the heat rays have any significance. The view of Sambon that thermic fever is due to an infection has not been accepted.

Pathology.—In sudden death from heat hyperpyrexia the necropsy may reveal nothing of note. The temperature of the cadaver is said to rise for a short time after death and may reach 114° F. (Manson). The early appearance of rigor mortis and putrefactive changes have been noted. The veins are engorged with dark and fluid blood. Loss of coagulability of the blood, according to Gihon, is a striking characteristic of heat stroke. When death occurs less suddenly œdema of the brain and meninges are common. Among 37 necropsies reported by McKenzie and LeCount[1] œdema of the brain alone was present in 22, œdema of the leptomeninges alone in 9, both were involved in 4, and hyperemia only in 3. The cerebrospinal fluid is clear and under pressure. The lungs are congested and œdematous. The spleen is soft and enlarged. Congestion, œdema and parenchymatous changes in the various organs, and capillary hemorrhages of the various mucous membranes and skin have been noted. Hemorrhages of the skin are common in that of the thorax, especially the sides below the axilla.

Symptoms.—Two principal forms are recognized. In *heat exhaustion* the patient becomes dizzy, weak, and usually collapses. The skin is pale and cool, the temperature normal or subnormal, the pulse rapid and feeble, and the respirations shallow and perhaps irregular. The pupils are dilated and react sluggishly. Cerebration is slow and mental confusion may be present. Syncope, partial or complete, is common. Usually after a short time recovery gradually takes place, during which the patient frequently complains of headache and a feeling of weakness.

In *heat hyperpyrexia* prodromata are not uncommon and consist of

[1] *Jour. Am. Med. Assn.*, 1918, **71**, 260.

malaise, headache, vertigo, somnolence, dry skin, and a frequent desire to urinate. The onset may be sudden, and without warning the individual staggers or falls unconscious, or evidences great mental excitation. The striking feature of the onset is the rapidly rising temperature which may reach 110° F. or higher. Instances as high as 114° F. have been observed. The pulse is rapid and full at first and later becomes weak and irregular. Headache, vertigo, dimness of vision, and sometimes nausea and vomiting are present. The conjunctivæ are congested and the pupils are usually contracted. Nervous symptoms are common. Delirium, stupor, coma, fibrillary twitching of muscles, and convulsions may occur. Delusions, hallucinations, homicidal and suicidal tendencies have been noted. Retention of urine occurs early and incontinence of urine and feces later with the loss of sphincter control. In the acute stages the knee jerk is almost always absent and does not return until the symptoms have cleared (Willcox). The urine is frequently scanty and contains albumin and casts. Diacetic acid and acetone are present in 12 per cent. of the cases (Manson). With deepening unconsciousness, the breathing becomes irregular or Cheyne-Stokes in type. Petechiæ of the skin may be present in severe cases.

Various clinical types have been described, dependent upon the predominance of certain groups of symptoms. The *asphyxial* type in which dyspnœa, cyanosis, and a feeble pulse are prominent. The *paralytic* or *apoplectic* type in which death occurs suddenly or within a few hours following the onset of coma with in some cases convulsions. Willcox recognizes a *gastric* type in which nausea and occasional vomiting with enlargement of the liver precede a rapidly fatal hyperpyrexia; a *choleraic* type in which the sudden onset of severe vomiting and purging with collapse are followed by death in three or four days; and *true heat hyperpyrexia* as described above.

Complications and Sequelæ.—Pulmonary œdema is not infrequently a terminal event. Reid[1] mentions pneumonia as being a fairly common complication. Heart weakness is common during the attack and may last for some days afterward. Susceptibility to heat may exist for a long time, slight exposure giving rise to headache and depression. After an attack difficulties of speech and impairment of memory are not uncommon; visual disturbances, such as diplopia and nystagmus, and multiple neuritis are among the rarer sequelæ. Insanity has resulted and symptoms of organic lesions of the brain and cerebellum have been noted.

Diagnosis.—Heat stroke must be distinguished from the unconsciousness of head injury, cerebral hemorrhage, uremia, diabetic coma, alcoholism, and opium poisoning. The history of exposure to high temperature, the past history of the patient so far as it may be obtainable, and the hyperpyrexia are important. In pontine hemorrhage with hyperpyrexia, the elevation of temperature occurs some hours after coma has developed, while the reverse happens in heat hyperpyrexia. In the tropics severe malarial infection with cerebral features may offer considerable difficulty. Reliance must be placed on the history, presence of splenic

[1] *Boston Med. and Surg. Jour.*, 1912, **67**, 217.

enlargement, and examination of the blood. Cerebrospinal fever is distinguished by the initial chill, herpes, irregular pupils, retraction of the neck, Kernig's sign, less high temperature range, examination of the spinal fluid, and duration.

Prognosis.—Patients with heat exhaustion usually recover. Heat hyperpyrexia is much more dangerous. The aged, alcoholics, and victims of debilitating diseases have a bad prognosis. Death may be due to respiratory or cardiac failure. A terminal œdema of the lungs is not uncommon. Prompt treatment reduces the mortality. The maximum temperature bears a relation to mortality. Among 12 cases with a maximum temperature of 107° to 108° F. there were 2 deaths; in 14 cases from 108° to 109° F., 5 deaths; 12 cases from 109° to 110° F., 5 deaths; and in 14 cases over 110° F., 6 deaths (Alexander[1]). Among British troops in Mesopotamia the mortality was 8 per cent. In hospitals where at times only the desperately ill are sent, the mortality may be high, as in the experience of the Cook County Hospital, Chicago, where in July, 1916, 70 deaths occurred among 158 patients.

Prophylaxis.—The avoidance of direct heat as much as possible, the restriction of work, an abundance of rest, the wearing of proper clothing and head covering, the avoidance of alcohol, the regulation of the diet with an abundance of water, avoidance of constipation, the use of fans, and the maintenance of physical fitness are personal preventive measures of importance. Improved ventilation and aëration of work places, lessened hours of labor, avoidance of overcrowding, the introduction of oil burners in the place of coal burning steamers, etc., have reduced the frequency of heat stroke in the occupations. In military life, the reduction of drills, especially in the middle of the day, the avoidance of long marches in close order, double canvas-top tents, etc., are prophylactic measures.

Treatment.—In heat hyperpyrexia the indications are to reduce the excessive temperature and promote elimination. The first is accomplished by the external use of cold either in the form of cold baths or ice-packs. Caution is necessary because the temperature may fall suddenly to below normal. It is well to stop the use of external cold in these forms when the temperature has dropped to 102° F. with a continuation of the use of the ice-cap. Ice-rubs are sometimes employed, but Leonard Hill has pointed out their inefficiency as compared with measures directed toward promoting evaporation from the body. This may be accomplished by fanning the body after sprinkling or sponging with cold water or covering with a wet sheet. Some have found the use of cold enemata beneficial. Elimination is favored by giving fluids freely by mouth if the patient is conscious or by hypodermoclysis. The intravenous use of saline or bicarbonate solution has been recommended. Venesection may be necessary if cyanosis is marked. As Osler has pointed out, this procedure probably saved the life of Weir Mitchell when he was a young man. Artificial respiration may be necessary. Lumbar puncture has been advised to relieve pressure. Bromides and chloral, or chloroform inhalations may be necessary to control delirium and convulsions. The cautious use of

[1] *Jour. Royal Army Med. Corps*, 1922, **38**, 358.

venesection, according to Manson, is the best way of controlling convulsions. The drug treatment is largely symptomatic with the avoidance of depressing cold tar products. The sudden drop in temperature with signs of collapse from too energetic hydrotherapy calls for supportive treatment. After the urgent symptoms have subsided a laxative should be given. During convalescence and for some time afterward rest, restricted exercise, and avoidance of heat should be insisted upon. The nervous sequelæ call for special care.

In heat exhaustion the indications are to support the patient and promote elimination. Absolute rest and quiet in a cool place are necessary. If the temperature is subnormal or if signs of collapse are present, external warmth is necessary. Gentle massage of the skin is beneficial. Caffeine and strychnine may be given hypodermically. Digitalis and camphor have been recommended. Water should be given freely by mouth and after the urgent symptoms have subsided calomel followed by a saline hastens convalescence. The after-care consists of rest, restricted exercise and the avoidance of exposure to heat.

Heat Cramps.—Hard muscular work in intense heat may give rise to muscular cramps affecting either the smaller muscles or the larger muscles of the extremities, and sometimes the abdominal muscles. Edsall[1] called attention to this condition in 1904. In his cases the cramps were preceded by a condition of muscular fibrillation. In a well-developed case the cramps may occur every two or three minutes, the interval increasing later to ten minutes or longer. They are accompanied by severe pain and dilated pupils. The attacks vary greatly in severity. The temperature is normal and the pulse seldom affected. The muscle spasms usually subside within twelve to thirty-six hours, after which the patient experiences muscle soreness upon slight exhaustion. Apart from some heart weakness which is said to be present, there is no evidence of disease of the organs. It differs from heat hyperpyrexia and heat exhaustion in the absence of thermal disturbances and the other phenomena of these conditions. The diagnosis from other conditions presenting muscular twitching, contractions or spasms, is not difficult. In strychnine poisoning, epilepsy, uremia, hysteria, etc., the toxemia or morbid condition presents many other phenomena of diagnostic value in differentiation. The *prognosis* is usually good, but a number of deaths have occurred. The *treatment* consists of rest in bed in a cool place and the administration of fluids freely. Warm baths have been recommended to relax spasm. Welsh[2] found that apomorphine in doses varying from $\frac{1}{2}$ to $\frac{1}{2}\frac{1}{0}$ gr. produces immediate relaxation.

COMPRESSED AIR ILLNESS[3]

Synonyms.—Caisson Disease, Divers' Paralysis, Aëropathy, The Bends.

[1] *Jour. Am. Med. Assn.*, 1908, **51**, 1969. [2] Ibid., 1909, **52**, 1178.

[3] The following references give a detailed discussion and bibliography: Keays, Compressed Air Illness, New York, 1909. S. Erdman, Compressed Air Illness, in "Industrial Health" by Kober and Hayhurst, Philadelphia, 1924. E. Levy, Compressed Air Illness and its Engineering Importance, Technical Paper 285, Bureau of Mines, Washington, D. C., 1922.

Definition.—Compressed air illness is the term applied to the phenomena which result when an individual returns too quickly to a normal atmospheric pressure after having been exposed to an excessive atmospheric pressure, such as may occur in compressed air chambers and in deep-sea diving. It is an occupational disease. The phenomena are proportionate to the degree of air pressure, the length of time exposed, and the rapidity of decompression. The symptoms occur within a few minutes to a few hours after decompression and are due to the liberation in the supersaturated tissues and fluids of the body of bubbles of nitrogen gas.

The earliest authentic recognition of compressed air illness is ascribed to Triger, the French engineer, who in 1839 elaborated the first practical caisson in mining coal under the Loire. With the development of the diving suit by Siebo in the early part of the Nineteenth Century, deep-sea salvage became possible and divers' paralysis made its appearance. The disease was quite common before the introduction of preventive measures; thus in the construction of the Danube Bridge in 1890, 47 per cent. of the men who worked at a maximum pressure of 32½ pounds developed the disease. Recent statistics, more accurately compiled on the basis of the number of decompressions, show a remarkable reduction in the incidence of the disease; thus in the East River Tunnel between 1904 and 1909 there were 557,000 decompressions with 3692 cases of illness, and 20 deaths. During the Public Service Commission tunnel work in New York from 1914 to 1921 there were 1,361,461 decompressions with 680 cases of compressed air illness and only two deaths.

Etiology and Pathology.—The disease occurs principally among divers, caisson workers, and those engaged in river tunnel construction. Divers frequently work at pressures of 53 pounds or more; while in river tunnel work, as in New York, the pressures may vary from 28 to 47½ pounds. When an individual is compressed by such pressures the fluid and tissues of the body become supersaturated with nitrogen. The saturation in general depends upon the amount of pressure and the length of time compressed; and specifically in certain body tissues on their absorptive capacity and vascularity. Pressures up to plus 27 pounds are not followed by serious developments (Japp), but every additional pound above plus 30 carries with it increasing risk (Erdman). The saturation of the tissues from the excess of nitrogen in the blood occurs gradually. It is not uniform, either in regard to the time required for saturation, or the amount of nitrogen taken up. Thus fatty tissue which is poorly vascularized saturates slowly, but can dissolve five times more nitrogen than blood or non-fatty tissue (Vernon). No disturbance is caused by the saturation *per se*. No disturbance is caused by decompression *if* this process is gradual so as to allow for slow desaturation of the nitrogen in the tissues. If decompression is rapid free bubbles of nitrogen gas form in the tissues and the blood. *The immediate cause of compressed air illness, therefore, is too rapid decompression.*

Mechanical injury to the tissues is produced by the expansion and coalescence of gas bubbles and by the formation of gas emboli. The fatty tissues are common sites for the accumulation of gas bubbles. The white

matter of the nervous system, composed as it is of fatty substance, and particularly those parts of it which are less liberally vascularized, such as the lower dorsal spinal cord, is the most common site of gas liberation. The subcutaneous tissues, the joints and their surrounding structures, are also common sites of the lesion. In the fatal cases autopsy reveals gas bubbles in the nervous system, liver, spleen, intestinal wall, and other tissues. Capillary hemorrhages may be present. Death may be due to pulmonary air embolism or gaseous distention of the right heart. Cross sections of the spinal cord may show areas of softening and capillary hemorrhages.

Individuals who are obese or physically unfit, and especially those with circulatory deficiency, are predisposed to compressed air illness. There is no evidence that the phenomena of the disease are related to atmospheric temperature or humidity, or to the presence of noxious gases, such as carbon dioxide, carbon monoxide, etc., which are seldom present in dangerous amounts.

Symptoms.[1]—The symptoms may be mild or severe and have their onset a few minutes to several hours after decompression. In the New York cases the onset occurred within one hour in 65 to 85 per cent. of the patients, and within three hours in 89 to 99 per cent. of the patients, and very rarely thereafter. In one group of 436 cases no onset of symptoms occurred after eighteen hours (Levy). Pain is the commonest symptom and occurred in about 90 per cent. of the cases either alone or in association with other symptoms. It is most frequent in the lower extremities and about the knees, giving rise to the workman's term, "the bends." The knee is kept in a semiflexed position and any attempt to straighten it aggravates the pain. The pain also occurs in the upper extremities, abdomen, etc., and may be associated with weakness, numbness, and paresthesias. Vertigo, "staggers," occurred in 5.3 per cent. of the cases (Keays). The symptoms referable to the central nervous system vary depending upon the area involved. Temporary weakness and numbness in the legs are common. In the more severe cases with involvement of the spinal cord, paraplegia, monoplegia, loss of sphincter control, and sensory disturbances occur. Involvement of the brain gives rise to headache, vertigo, speech disturbances, vomiting, drowsiness, collapse, coma, hemiplegia, monoplegia, convulsions, etc. Involvement of the cranial nerves gives rise to nystagmus, diplopia, aural vertigo, deafness, etc. Dyspnœa, "chokes," or a sense of constriction in the chest, occurs in less than 2 per cent. of the patients (Keays) and is probably due to pulmonary air embolism.

The paraplegia of the disease usually involves the lower extremities.

[1] Two interesting groups of patients have been analyzed with regard to the frequency of symptoms. Keays' classification of 3692 cases among 557,000 decompressions from 1904 to 1909 in the construction of the Pennsylvania Tunnel, New York, and a more recent one of Levy of 680 cases occurring among 1,361,461 decompressions during Public Service tunnel construction work in New York from 1914 to 1921. In the latter group of 680 cases 624, or 91.8 per cent., had localized pain; 44, or 6.5 per cent., vertigo; 11, or 1.6 per cent., affections of the central nervous system; 1 case, or 0.1 per cent., had dyspnœa. In 251, or 37 per cent. of the cases, there was multiple joint involvement; and in 38, or 5.6 per cent. there were body or head pains. Only 1 case of localized pain in the abdomen and collapse occurred, which ended fatally. The 1 case of dyspnœa ended fatally. Two deaths only occurred.

It comes on rapidly and may be of any degree of severity, from a slight and temporary condition to a permanent affair, There is no general relation between the pain and the paralysis, as either may occur without the other. Peripheral pains have been noted even when there was total loss of pain sensibility from cord lesions.

Prognosis.—In one series of 3692 patients there were 20 deaths or a mortality of 0.54 per cent. (Keays); in another of 680 patients there were 2 deaths (Levy). In Keays' series, apart from those dying within eight days, there were 10 cases of permanent paralysis, or 0.3 per cent. of the total cases. Of these, 4 died within five months. In Levy's series 2 cases of paralysis resulted in permanent disability. The present day low mortality is attributed to the enforcement of gradual decompression and prompt recompression when symptoms develop.

Prophylaxis.—This consists of care in the selection of physically fit employes, restriction of the number of hours of work in relation to the degree of pressure to which the workman is exposed, and the enforcement of graduated decompression. New York, New Jersey, and Pennsylvania have regulatory laws governing compressed air operations. The British Admiralty has formulated regulations regarding the decompression of divers.[1] In caisson work it is interesting to note the influence of prophylaxis as applied today. In the construction of the Hudson Tunnel in 1885 there was a mortality of 18 per cent.; in 1904 to 1921, in New York tunnels the mortality was less than 0.5 per cent.

Treatment.—Caisson workers themselves found out early that the only remedy when symptoms developed was to reënter the compression chamber. A medical air lock or recompression chamber should be available in all caisson work and on ships engaged in deep salvage. When the ill worker is placed in the compression chamber, the pressure is rapidly raised to that in which he had previously worked. He should be kept at this pressure for some time, depending upon the severity of his symptoms, and then gradually decompressed. The results of decompression are striking. Among 3692 cases, 90 per cent. were completely relieved, 9 per cent. partially relieved, and less than 1 per cent. failed to get any relief.

ALTITUDE SICKNESS[2]

Synonyms.—Mountain Sickness, Anoxemia, Air Sickness.

At certain heights above the sea level an individual exposed to an atmosphere in which the partial pressure of oxygen is greatly reduced, develops a series of phenomena to which the term altitude sickness is given. An

[1] A diver working at 140 feet, for example, is raised at once to a depth of 50 feet where he waits ten minutes, then to 40 feet for ten minutes, 30 feet for twenty minutes, 20 feet for thirty minutes, 10 feet for thirty-five minutes and then is allowed to leave the water.

[2] Air Service Medical issued by U. S. War Dept., Division of Military Aëronautics, Washington, D. C., 1919; and Air Service Information Circular, same, August 15, 1920.

The Medical Problems of Flying. Reports i to viii of the Air Medical Investigation Committee, Medical Research Council, London, 1920.

Medical and Surgical Aspects of Aviation, by H. G. Anderson, Oxford Medical Publications, London, 1919.

Air Sickness, Its Nature and Treatment, by Cruchet and Moulinier, London, 1920.

Acclimatization to High Altitudes, by J. S. Haldane, *British Med. Jour.*, 1924, ii, 885.

elevation of 10,000 feet or less might provoke the malady in some, others may escape the symptoms up to 14,000 feet, while only a very few can venture without distress to 19,000 feet and higher. The phenomena of altitude sickness vary in different individuals depending on their physical fitness, and in the same individual, depending upon (1) the suddenness of the ascent, (2) the lowness of the atmospheric pressure (the altitude), and (3) the physical exertion made in ascending, that is, whether performed by climbing or by passive carriage on horse, railway train, or in an aëroplane. The phenomena have been observed in balloonists, aviators, mountain climbers, and experimentally in individuals breathing in closed chambers under various degrees of reduced oxygen pressure.

Paul Bert in 1878 first clearly demonstrated experimentally that the essential factor was an imperfect oxygenation of the blood. Other observers, such as Mosso, attributed the symptoms to a lack of carbon dioxide, while Kronecker believed in mechanical factors. Recent workers have confirmed Bert's conclusions.

Pathological Physiology.—As a result of the lowered partial pressure of the atmospheric oxygen there occurs a lowered partial pressure of the oxygen in the blood (anoxemia). The blood reaching the tissues may still contain an abundance of dissociable oxygen, but the pressure is too low and the observed symptoms are due to low oxygen pressure and not merely insufficiency in the amount of oxygen in the blood (Haldane). As a result of the reduction in oxygen pressure the respiratory and cardiac centres are stimulated. The respirations are deeper, the heart-rate is accelerated, and the blood flow more rapid. Corbett and Bazett found the normal reaction to an oxygen want corresponding to about 18,000 feet to be an increase of about 30 per cent. in the pulse-rate, about 36 per cent. in the pulse-pressure, and 50 per cent. in pulmonary ventilation. The pulse-pressure rise is brought about mainly by a drop in diastolic pressure. When failure to stand oxygen want occurs the adaptive mechanisms of respiration and circulation may be at fault. However, symptoms of oxygen want may occur in rare cases at altitudes below 10,000 feet in individuals apparently healthy.

Death may occur in sudden ascents to great heights, as in the ill-fated balloon ascent to 28,820 feet described in 1875 by Tessaudner, in which his two associates died. If the reduction in the partial pressure of oxygen is gradual, as was demonstrated in the Mount Everest Expedition of 1924, symptoms may be prevented or the more serious effects modified so that greater heights may be reached with a greater safety than was formerly thought possible. This *acclimatization* to higher altitudes has been studied by Haldane who believes that the alveolar epithelium plays an important part by "actively driving oxygen inward into the blood," and thus compensating for the low oxygen pressure in the inspired air. Another compensating factor is the concentration of the hemoglobin in the blood and an increase in the red cells. A 10 per cent. rise in the hemoglobin ratio to blood volume may occur in twenty minutes (Collier). That an active concentration of blood occurs during the first few days of residence at high altitudes was demonstrated in the Pike's Peak investigation. One of the subjects had an increase of 15 per cent. in hemoglobin

and a decrease of 10.8 per cent. in total blood volume. Following the initial rapid increase in hemoglobin and red cells ascribed to mobilization of red cells and in part to concentration from loss of fluid from the blood, there occurs a true erythremia due to an increased activity of the blood-forming organs. In the Mount Everest Expedition of 1924 an increase of the red corpuscles from 4,480,000 at 700 feet to 8,320,000 at 18,000 feet was noted (Hingston).

Recent experimental observations by Haldane and his associates indicate that during oxygen want an alkalosis is present. The adaptive mechanisms are less efficient in those who are in ill health, overworked, undernourished, or the victims of disease. In such individuals altitude sickness is prone to be more common and more severe. It should be kept in mind that certain of the symptoms, such as giddiness, vomiting, and fainting in the air, etc., may occur from many different causes apart from the physical and chemical deficiencies in the atmosphere. As Head points out, in regard to aviators, conscious stability and comfort in the air depend primarily on normal responses in three groups of sense organs, the vestibular apparatus, the eyes, and the proprio-receptive system with its endings in the muscles, bones, and joints.

Symptoms.—The acute onset of serious symptoms at very high altitudes quickly reached is dramatically recorded in the balloon ascent of Glaisher and Coxwell in 1862. Glaisher first noticed at an altitude of about 26,000 feet that he could not read his instrument properly. Shortly afterward his legs were paralyzed and then his arms, though he could still move his head. Then his sight failed entirely and afterward his hearing and he became unconscious. His companion meanwhile found that his arms were paralyzed, but that he was still able to seize and pull the rope of a valve with his teeth which permitted gas to escape and the balloon to descend. As Glaisher recovered consciousness, he first heard his companion's voice and then was able to see him, after which he quickly recovered. The balloon, during the ascent, reached an altitude of about 30,000 feet.

Among aviators the symptoms noticeable while *in the air* are dyspnœa, rapid pulse, muscular weakness, frequent desire to urinate, and impairment of judgment and perception. Very few pilots breathe through the nose above 12,000 feet. The frontal headache sometimes comes on while in the air, but more commonly after landing. Vomiting is very rare and hemorrhage from the mucous membranes is practically unknown (Birley). Disturbances of mental function may occur and are characterized in some instances by a sense of nervous exaltation giving a false sense of security; and in other instances by loss of memory and confusion. "The skilled photographic observer takes eighteen photographs upon the same plate, the observer throws his valuable notes overboard, the pilot makes for a wrong destination or goes to sleep, and the fighting scout forgets to go into action" (Collier). The most important symptom *after landing* is fatigue. Reports are laboriously made out, the gait is often unsteady and labored, and the general sense of lassitude is reflected in the face and general demeanor. Buzzing in the ears is not uncommon and dizziness may occur. Frontal headache comes on shortly after landing and persists

for a few hours to twenty-four hours or more. In some instances the memory is confused as to what has happened during the fly.

Aëro neurosis (Flack), or aviator's neurasthenia, are terms applied to the neurasthenia which develops in those engaged in flying. It is not unlike the neurasthenia encountered in other conditions (Cruchet), and is frequently the result of simple overwork. It is characterized by headaches, disturbed sleep, insomnia, fits of irritability and depression, and easy fatigue.

Among mountain climbers the symptoms develop less rapidly. In the Mount Everest Expedition in 1924, Hingston[1] reports that shortness of breath was definitely felt at 14,000 feet and became increasingly marked until the slightest exertion was accompanied by respiratory distress at 21,000 feet. At 28,000 feet breathing became so difficult that the climber had to rest every 20 or 30 yards and a vertical ascent of 100 feet was as much as could be accomplished in an hour's climb. Instances of Cheyne-Stokes breathing were frequently observed during sleep. Inflammation of the air passages was common. The pulse-rate was increased in proportion to the altitude. Cyanosis of the lips and finger nails was frequently observed above 18,000 feet. Headache was common and increased by exercise and stooping. Giddiness occurred in some, but there were no instances of actual fainting. There was no instance of hemorrhage from any of the mucous membranes. Frost bite occurred in a number of cases. Sleep was difficult at high altitudes and it was advisable to keep the head raised to ease the breathing. There was much loss of muscular power, and above 15,000 feet persistent loss of weight. The appetite was impaired and sweets were preferred to meats. There was no nausea and vomiting. Diarrhœa in some instances was very persistent. There was none of the impairment of judgment noted by aviators. There was, however, a mental lassitude and forgetfulness, and at the highest altitudes all mental effort was a burden. Mild tremors occurred in a few of the climbers. Acclimatization was associated with diminution of the symptoms and those who had been on previous expeditions suffered less.

Prophylaxis and Treatment.—Various tests have been devised, especially for aviators, to determine physical fitness for altitude ascents. These are described in special monographs. (See foot-note, p. 633.) Repeated physical examinations are important to determine the continuance of fitness. The introduction of the use of oxygen by means of such special devices as the Dreyer apparatus which automatically delivers oxygen in inverse proportion to the barometric pressure, has enabled aviators to keep at greater heights for longer periods in greater comfort and with greater efficiency. Special suits have been devised to protect against cold. The use of oxygen after landing lessens the after effects of the flight. When symptoms develop return from the altitude is indicated. Among the mountain climbers of the Mount Everest Expedition, 28,000 feet were reached without the use of oxygen inhalations, indicating that acclimatization occurs in gradual ascents. The development of symptoms among mountain climbers requires the immediate cessation of exertion, the use of oxygen if available, and prompt return to lower levels.

[1] *British Med. Jour.*, 1924, ii, 1124.

THE UNTOWARD EFFECTS OF ELECTRICAL CURRENTS[1]

The untoward effects of electricity occur as the result of exposure to (1) industrial currents, (2) lightning, and (3) radiant energy in the form of the roentgen-rays.

Industrial Currents.—There were 816 deaths from accidental electrical shocks in the U. S. Registration Area in 1922. They were divided almost evenly between the cities and rural districts and about 30 times more common in men than in women. The relative frequency of electrical injuries among workmen may be obtained from statistics of Workman's Compensation Bureaus. In Pennsylvania in 1924 there were 1170 accidents reported as due to electricity, of which 88 were fatal and 1082 non-fatal. As compared to all forms of industrial accidents, 1 in each 150 were directly due to industrial currents; and 3.2 per cent. of the total time lost from work was due to the same cause. The greatest number of cases occurred among those employed by the public utilities, in metal producing, and in mines. The frequency of electrical fatalities in relation to other common causes of death among electrical workers is shown in the following table:

RECORD OF ACCIDENTS AND DEATHS BY OCCUPATIONAL DISEASE FOR INTERNATIONAL BROTHERHOOD OF ELECTRICAL WORKERS.[2]

	Linemen.	Inside-men.	Miscellaneous.*	Total.
1922				
Electrocution	23	7	1	31
Falls (fractures, breaks)	9	4	..	13
Burns (explosions, etc.)	4	..	..	4
Miscellaneous (drowning vehicular)	3	5	3	11
Tuberculosis	9	18	6	33
Pneumonia	3	11	3	17
Total				109
1923				
Electrocution	12	10	7	29
Falls, etc.	5	7	..	12
Burns, etc.	3	3	..	6
Miscellaneous	6	11	..	17
Tuberculosis	7	19	5	31
Pneumonia	5	14	1	20
Total				115
1924				
Electrocution	29	11	5	45
Falls, etc.	13	11	4	28
Burns, etc.	4	1	1	6
Miscellaneous	2	7	2	11
Tuberculosis	5	22	1	28
Pneumonia	7	23	..	30
Total				148

* Includes all branches of trade except linemen and insidemen.

[1] *Historical Note:* The first loss of life from an industrial current occurred in 1879 when a stage carpenter was killed at Lyon by the alternating current of a Siemens dynamo that was giving a voltage of 250 volts at the time. This is interesting in view of the use of electricity in lighting the operatic stage as long ago as 1849 in Paris; and the use of electricity in light-houses on and off the Coast of England since 1857. The first death in England occurred in 1880 (Goulstonian Lectures, 1913, by A. J. Jex-Blake).

[2] *Jour. of Electrical Workers and Operators*, 1925, **24**, 213.

Apart from industrial accidents, there are many fatalities recorded due to contact with the ordinary 110-volt lighting circuits used in homes.

Injuries from electrical currents may result from flashes or actual contact. *Flashes* or arcs occur upon breaking or short circuiting currents, for example, in the handling of switches, the crossing of faultily insulated wires, or where a piece of metal, such as a tool, falls across exposed wires or a switch board. A flash from a high voltage conductor has been known to jump some distance from the switch board and envelope a man in flames. Flash injuries *per se* must not be confused with the irritation which follows continued exposure, often at a distance, to the electric arc, such as occurs in electric welding. Such irritation is frequently evident in the eyes and is due to the actinic, rather than the heat rays and is called electric ophthalmia. The symptoms are those of conjunctivitis with photophobia and profuse secretion of tears. Flash injuries are the result of heat which produces painful burns of the unprotected parts.

Contact injuries are manifested by local phenomena (burns) or general phenomena (shocks) or both. These are not necessarily related. In one patient the heat effects may predominate; in another, as witnessed in accidental electrocution, there may be no demonstrable local lesion. Oliver saw a youth severely burned as the result of contact with 6000 volts, but without fatal consequences. In other instances extensive disfigurement may occur. The loss of a hand, or arm, or leg, or several of the extremities have been reported, with recovery. The *shock* manifestations vary greatly depending upon many external and individual conditions. Generally speaking, the higher the voltage, the greater will be the current through the body, and the longer the duration of contact the greater the danger to life. No current of 50 volts or over is safe. Direct contact is necessary in low voltages, but in high voltages the current may jump or spark. Direct *contact* with a voltage in excess of 15,000 is seldom possible unless the workman falls over the current, since the voltage jumps to the fingers, flexing them and making contact impossible. Such an individual may fall to the ground or be thrown away. There is no graded relationship of voltage to shock, since experience has revealed that an exposure to the shock of 95 volts may be fatal, while an exposure to 6000 volts has been recovered from. It is generally believed that alternating currents are more dangerous than direct currents, although this is not accepted by all observers. The individual factors are important. These are principally the resistance of the skin and body; and the path of the current through the body or over the surface of the skin. The dry skin is a poor conductor and callousness of the hands may offer a high electrical resistance. Wetting of the skin lessens resistance and an electrical current which is able to pass the skin becomes dangerous. A case in point is that of a man standing on a wet bath mat fixing an electric light socket with wet hands. The moisture minimized skin resistance and the shock was such as to cause violent contraction of the muscles of the hand, an inability to release the grip, and a fatal result. A continuous contact with low voltage may cause muscular contractions in other portions of the body; of the thorax with inability to breathe, of the skeletal muscles with spasms and pains; of the heart with resulting ventricular fibrillation and death. The blood is a good conductor and the maximum

damage in high voltage is probably in the central nervous system as the result of electrolysis in the smallest bloodvessels (see Pathology). Death in such cases may occur suddenly as a result of arrest of respiration or circulation, or both.

A study of the *pathological physiology* of shock would indicate, to quote Oliver, that death may be only apparent at first. The sudden inhibition of respiration may not be due to permanent damage of the respiratory centre. The sudden stoppage of circulation may not be due to irrecoverable ventricular fibrillation (Drinker). If artificial respiration is resorted to the dangers of asphyxia may be held in abeyance until such time as the respiratory centre recovers. Such recovery, if the circulation is adequate, has been observed after several hours. The real problem of the circulation in electrical shock is concerned with the heart which may stop at the same time as the arrest of respiration or conceivably without any relation to the respiration, as the direct result of ventricular fibrillation; or later as a result of asphyxia, the indirect result of respiratory failure. As will be emphasized under treatment, artificial respiration is the vital part of the accepted method of resuscitation.

Pathology.—The local lesions resemble burns from other causes and vary in degree from slight superficial involvement to extensive involvement of deeper tissues with ashing of bone. In addition to these changes Jellinek[1] describes as "metallization," a discoloration which varies from a yellowish-brown due to copper, to a brownish-black due to iron. He considers that the electrical current mark, if not merged with the burn, may be distinguished by certain characteristics. It is usually small, round, and pale yellow. It remains for weeks, and then is cast off together with necrotic tissues, to give way to a highly vascularized granulation which remains soft and never loses the vascularization to form a firm scar.

The pathology of shock has been studied by various observers and notably by Spitzka, in relation to penal electrocution. He states that at the moment of contact the body stiffens to a state of tonic muscular spasm which abates as soon as the voltage is reduced, to again attain its maximum with each rise of voltage. When the current is interrupted the body collapses. The temperature rises promptly to 120° to 129° F. within twenty minutes, the result of increased tissue metabolism in a body in which the vital mechanisms of heat dissipation (respiration, circulation, etc.) have been abolished. Furthermore, the release of 10 to 20 horsepower of energy within the body contributes to the caloric increase. The heart is flaccid when first exposed, but soon contracts and assumes a tetanized condition. The lungs are devoid of blood and weigh 7 or 8 ounces; much less than ordinarily found. The blood is of a dark brownish hue and rarely coagulates, the fibrinogen or the fibrin ferment, or both, are destroyed (Spitzka). The maximum damage is apparently in the central nervous system. Microscopic studies of the brain (Spitzka and Radasch) reveal curious circular lesions varying in size from 25 to 300 microns and characterized by a central rarified part and a peripheral condensed zone. The most characteristic areas show a bloodvessel surrounded by a delicate small meshed reticulum respresenting the central

[1] *Wien. Klin. Wchnschr.*, 1923, **36**, 157, abstract *Jour. of Indust. Hyg.*, 1924, **5**, 127.

four-fifths of the area. The fibres are in the main radially directed. The peripheral zone appears condensed and composed of circularly arranged strata. These lesions are longest and most characteristic in the brain stem. In some sections the bead-like arrangement of the lesions along the bloodvessel, as well as their individual characteristics, suggest the sudden liberation of bubbles of gas due to electrolytic properties of the current as it seeks the path of least resistance along the bloodvessels. The maximum number of lesions are found in the most constricted parts of the brain stem in the path of the current and are most numerous along the longitudinal fibre tracts and bloodvessels.

Various observers have found minute hemorrhages in the brain and various organs.

Symptoms and Sequelæ.—The symptoms have to some extent been discussed in the preceding paragraphs. The local phenomena of burns and tissue destruction, and the general phenomena of shock are of wide diversity. The muscle spasms, if the patient has not been rendered unconscious, may cause great pain and terror. Syncope is common and is usually associated with arrested respiration. The pulse may be weak, rapid, scarcely perceptible, or absent. The unconsciousness may be transient or exist for some hours, life being continued by artificial respiration. With the return of consciousness recovery may be rapid and complete, but sometimes various nervous disturbances follow. In the latter case there is usually a state of hebetude for several days, accompanied by weakness, headache, and sometimes palpitation of the heart. In some cases there is a state of mental confusion or delirium, tremor, and a general depression of the nervous system similar to that following other forms of severe traumatism. Amnesia and various psychoses have been observed but the mental disturbances were transient. Functional nervous diseases, as hysteria and neurasthenia, are common occurrences after an electrical shock. Abundant examples of either of these two neuroses, or of a combination of both, are found in the literature. Epileptiform and apoplectiform seizures are reported. Bulbar symptoms, transient in character, were reported in a few cases, but in view of their temporary nature they were probably cases of functional neuroses. Mills reported 2 cases in which there cannot be any doubt as to the organic character of the involvement of the medulla. There are also records of apparently undoubted cases of hemiplegia, spastic paraplegia, and disseminated sclerosis, following shocks from various electric sources, but these records are clinical. The pathological findings of those few cases that come to autopsy are in general negative, except a few capillary hemorrhages or small cellular changes in some cases.

Eye disturbances have been observed by various authors. Dimness of vision, ptosis, contraction of pupils, sluggish reflex reactions, subconjunctival ecchymoses, corneal opacity, are among the external ocular changes reported. In a certain number of cases profound alterations of the eye were noticed, *e. g.*, hemorrhages in the retina, with pigmentation, tearing, bleeding, and rupture of the choroid, iridocyclitis, luxation of the retina, anemia of the optic nerve, optic atrophy, and blindness. There are reports of the formation of cataract. Hess observed, experimentally, cataract formation in animals. Disturbances of the auditory apparatus

occur and pain in the ear, with impairment of hearing, is a frequent symptom following electric shock.

Treatment.—*Prophylaxis* consists of the persistent use of safety devices and the education of workmen and others in the dangers incurred by exposure to electrical currents. The treatment of burns and wounds is along ordinary surgical lines. If the shock has been slight and the patient conscious, no special treatment apart from rest is required. If excitement is present sedatives, such as the bromides and chloral, may be necessary. The rules for resuscitation[1] are as follows: (1) *Immediately break the circuit.* With a single quick motion free the victim from the current. Use any dry non-conductor (clothing, rope, board) to move either the victim or the wire. Beware of using metal or any moist material. While freeing the victim have every effort made to shut off the current quickly. (2) *Instantly apply artificial respiration.* As soon as the victim is clear of the conductor, rapidly feel in his mouth for any foreign body (tobacco, false teeth, etc.) and after removal begin artificial respiration at once. The Schaefer method consists of the following: (*a*) Lay the subject on his belly, with arms extended as straight forward as possible, and with face to one side, so that nose and mouth are free for breathing. An assistant draws forward the subject's tongue. (*b*) Kneel straddling the subject's thighs and facing his head; rest the palms of the hands on the loins with fingers spread over the lowest ribs. (*c*) With arms held straight, swing forward slowly so that the weight of your body is gradually but not violently, brought to bear upon the subject. This act should take from two to three seconds. (*d*) Then immediately swing backward so as to remove the pressure. (*e*) Repeat deliberately 12 to 15 times a minute the swinging forward and backward, a complete respiration in four or five seconds. As soon as artificial respiration has been started, and while it is being continued, an assistant should loosen any tight clothing about the subject's neck, chest, or waist.

The artificial respiration should be continued without interruption (if necessary two hours or longer) until natural breathing is restored. If natural breathing stops after being restored use artificial respiration again. There is no justification for the use of various mechanical devices which are inferior to the Schaefer method. The only active remedial measure found useful in ventricular fibrillation is cardiac massage through the diaphragm, but this is obviously not available under the conditions in which electric shocks occur (MacWilliam). When heart massage is applicable it is rendered more effective by the intracardiac injection of epinephrine.

Lightning.—There were 425 deaths from lightning in the U. S. Registration Area for 1922. The fatalities were nineteen times more frequent in the rural districts than in the cities, and about four times more common in men than in women. Although accurate statistics are not available, DaCosta estimates that at least 5 are injured from lightning to each 1 killed. Jack records an instance in which a church was struck; 300 people

[1] Commission on Resuscitation from Electric Shock, representing the American Medical Association, National Electric Light Association and American Institute of Electrical Engineers; also C. K. Drinker on The Present Status of the Problem of Resuscitation in Cases of Electric Shock, etc., *Jour. of Indust. Hyg.*, 1923, **5**, No. 1, 255.

were in it, 100 were injured and mostly made unconscious, 30 had to take to their beds, but only 6 were killed. As many as 18 persons have been killed by a single stroke of lightning (Hofmann).

Jex-Blake[1] calls attention to one feature of lightning flashes that distinguishes them from ordinary industrial electric currents. "Given a choice of several alternative paths to travel along, ordinary industrial currents travel along them all in quantities directly proportional to their conductances, or as it is more usually put, inversely as their resistances. But the very brief alternating current obtained by discharging a charged Leyden jar behaves quite differently; for it will leave a good conductor such as a coiled up thick copper rod in order to spark across an extremely badly conducting air space, preferring a path of low self-inductance to one of low resistance. The same is true of lightning, as was first emphasized by Lodge; it explains the tendency of lightning to send side-flashes out of good conductors like lightning rods into any objects nearby, and the frequent failure of such rods to protect buildings from damage by lightning."

After lightning stroke no external or internal lesion may be found. In other instances marked damage to the body is present and the clothing is found torn and perhaps distributed in fragments some distance from the body. The foot wear commonly suffers most, probably by its immediate contact with the earth and possibly as the result of changes in its conductivity and of irregularity of moisture in its interstices. The effects of lightning are most varied and curious. The lightning discharge coming in contact with the body may spread itself over the surface of the body, the resistance of the skin preventing penetration. The result may be a superficial burn of small or large size and of curious configuration. These lightning figures consist of reddish-brown or purplish discolorations which in their outline have a fancied resemblance to shrubbery, branches of trees, landscapes, geographical maps, etc. In other instances the burn is deeper with injury of the muscles, bones, and viscera. Patches of skin and hair may be torn off. The ear drum may be lacerated. Fracture of bones is not uncommon and open wounds of the skull, thorax, and abdomen, and rupture of the internal organs, such as the diaphragm, heart, and intestines have been reported. Death of the fetus in utero while the mother was only stunned, and the death of the mother while carrying a child which was unharmed, have occurred.

In one patient seen by DaCosta the man was burned and wounded from his left shoulder to his left heel; the clothing was scorched, keys and money in the pocket were fused, and the shoe torn from the foot. The patient recovered. In most instances, however, direct strokes passing through the body are fatal. Two persons struck by the same bolt may show the greatest diversity in the electrical effects. This may be difficult to understand by the medical man unacquainted with electrical phenomena. The difference in conductivity of wet and dry portions of the clothing, the lessened resistance to penetration of the body when the skin is wet, the portion of the body struck, are all factors which influence the course of the electrical discharge through the body. Induction effects

[1] The Goulstonian Lectures on Death by Electric Currents and by Lightning, *British Med. Jour.*, 1913, i, 425, 492, 548, 601.

may occur by proximity to an object, such as a tree which has been struck by lightning, or an injury may result by the jumping of the current from the tree to the body after the manner of flashes or arcs which occur on exposure to high voltage industrial currents.

If the amount of electricity contained in a lightning charge which reaches the body is small, the shock may be slight and of short duration. The individual is stunned and perhaps temporarily unconscious. Recovery is prompt and except for the slow disappearance of fright is not associated with any untoward effects. In the more serious cases breathing is arrested, unconsciousness is complete, the pulse is rapid and feeble, scarcely perceptible or absent, and death may ensue. If recovery occurs the same sequelæ with regard to the nervous system may develop as in electrical injuries due to industrial currents.

Treatment.—Resuscitation from lightning is the same as from electrical currents. Artificial respiration by Schaefer's method should be resorted to immediately. For the various injuries encountered the treatment is along surgical lines.

Injurious Roentgen-ray Effects.—The discovery of the use of the roentgen-ray in the diagnosis and treatment of disease is one of the remarkable achievements of medical science. At first thought to be relatively harmless, it was soon found to be dangerous from too long or too frequent exposure and too close proximity to the tube. The roentgen-ray operators themselves were among the early sufferers and not a few of them died from roentgen-ray cancer.[1] The roentgen-ray injuries have been widely studied and numerous extensive articles upon the subject may be found in special articles and monographs. The baneful effects are local and general.

Local Effects.—These are usually manifest in the skin and vary from a mild erythema to necrosis with destruction of the deeper tissues. The necrosis is the result of obliterative changes in the bloodvessels with resultant impairment of local nutrition. In the mildest form an erythema appears which in the course of several days disappears without any after-effect. If the exposures are frequently repeated the erythema is succeeded by a freckling or diffuse pigmentation. In some instances a downy growth of hair is noticed, or in the hairy parts, a loss of hair which is followed by a regrowth. In the severe forms of injury the erythema is associated with an ill-defined vesiculation with the subjective symptoms of skin irritation and is followed by a dry branny, or in some instances, a larger scaly desquamation. Among roentgen-ray operators frequent exposure of the hands gives rise to an erythemato-squamous condition which persists and is associated with varying degrees of pigmentation, wrinkling, and atrophic changes in the skin. The nails become thin and brittle. Keratoses may develop which are prone to eventuate in malignant changes. A more serious local effect of overdosage of the roentgen-ray is a local destructive lesion characterized by an erythema with vesiculation which is followed by necrosis of tissue to varying depths with the formation of a slough which when removed exposes a deep ulcer. This ulcer is described as "shallow, sluggish-looking,

[1] Cole, H. N.: *Jour. Am. Med. Assn.*, 1925, **84**, 865.

with a slightly or moderately hyperemic or inflammatory border, and covered with a rather adherent grayish, often tough and leathery crust or membrane; it is persistent with but little if any tendency to spontaneous reparative change, and the accompanying pain is often excruciating." (Stelwagon).

A chronic roentgen-ray neuritis has been described; and among operators, the bones of the hands, especially of the fingers, may show definite changes with actual absorption of osseous tissue (Cole).

General Effects.—These are seen most often in patients who are receiving intensive roentgen-ray treatment, as for example in inoperable cancer. The most striking changes occur in the blood. As Minot and Spurling[1] point out, it has long been recognized that desirable therapeutic irradiation produces slight blood alterations, and that excessive irradiation may produce a profound change in the hematopoietic system. In 1904 Heineke demonstrated that the lymphoid tissue of the body was primarily affected with a diminution in the number of lymphocytes in the blood. The location of the roentgen-ray exposures bears no specific relationship to the blood changes induced. The extent of the surface exposed, however, is of considerable importance and is more important relatively than the dose of the rays. If the irradiation is sufficiently large a complete aplasia of bone-marrow with the characteristic blood picture may be produced. This does not occur if the therapeutic use of the roentgen-ray is guarded. On the other hand, the customary therapeutic dose is not infrequently associated with a decrease in the number of white cells, especially the lymphocytes, so that leukopenia and lymphopenia may occur. Preceding the decrease in the white count a transient increase develops due to an increment of polymorphonuclears. A very small dose may cause a lymphocytosis. An eosinophilia of from 7 to 23 per cent. is usual after repeated exposure to the rays (Minot and Spurling). The importance of a knowledge of the blood changes consists in the recognition of those minor changes which are offset by the benefits of irradiation in cancer, etc., and of the dangers of too intensive irradiation in a patient who has a leukopenia or marked evidences of defective blood formation.

Prophylaxis.—The protection of operators is especially important. The Royal College of Physicians and the American Roentgen Ray Society have issued reports[2] regarding safety measures.

Treatment.—The local treatment of roentgen-ray erythema is along ordinary lines. The ordinary palliative applications, dusting powders, and alkaline sedative lotions, as in use in acute dermatitis, are indicated. The ulcerating lesions are treated as in general. Dodd's solution (phenol, 1.85 parts; zinc oxide, 15.5; glycerine, 4; lime water, sufficient to make 250) is excellent for use in the acute stages (Cole). In the chronic stages with induration, keratoses and ulceration, treatment is difficult. The possibility of malignancy and the necessity for surgical treatment must be considered. Carbon dioxide snow, electrocoagulation and the ultraviolet quartz light have been recommended for indolent lesions. Surgical excision and skin grafting may be necessary. The treatment of the general effects is obvious.

[1] *Am. Jour. Med. Sci.*, 1924, **168**, 215. This article contains a comprehensive bibliography.
[2] *Brit. Jour. Radiol.*, vol. **29**, 282; *Jour. Roentgenol.*, 1923, **10**, 246.

PART VI

DISEASES DUE TO CHEMICAL AND ORGANIC AGENTS

CHAPTER XXI

CHRONIC LEAD, ARSENIC, MERCURY, PHOSPHORUS, ZINC, COPPER, BRASS, MANGANESE BISMUTH, AND SILVER POISONING.

By NORMAN B. GWYN, M.B.

Introduction.—Disorders the result of intoxication by metals, fumes, dusts and gases belong to the great new field of industrial medicine. Medicine proper has most concern with some forms of poisoning resulting from exposure on the part of the patient and for years has been familiar with certain disease pictures seen in workers in metals and chemicals. Each year sees new conditions arising as new trade processes develop but in a work of this kind we must confine our attention to the more persistent and usual intoxications.

In America the study of the disorders incident to working in a dangerous trade is now carried on in such extensive form by private, Federal and State efforts that an excellent survey of "Industrial poisonings" can readily be made by consulting such publications as the Journal of Industrial hygiene, the reports from the U. S. Department of Labor (Bureau of labor statistics) the U. S. Public Health reports and the reprints of the department of the Interior (Bureau of Mines). The health departments in certain States as Ohio, Illinois, New York, Massachusetts and Pennsylvania have issued papers and bulletins on most phases of occupational diseases, and State control in "dangerous trades" seems to be in process of arriving. The activities of industrial clinics, laboratories of physiology, biological chemistry and pharmacology in many of the clinics are now represented by contributions on the hygiene and dangers of trade which have placed the study of such matters in this continent on a firm basis. I have drawn freely from the findings of the U. S. Bureaus, from the publications of the Industrial Clinic at the Massachusetts General Hospital, from the work of the laboratories of physiology and hygiene at Harvard, and from the remarkable collections and publications of Hutton, Alice Hamilton, Hayhurst, Legge, Goadby and others.

CHRONIC LEAD POISONING

In clinical and economic importance, lead poisoning largely overshadows all other chronic intoxications except that due to alcohol. From the economist's standpoint it is noteworthy that no chemical so readily capable, in its ordinary uses, of causing chronic poisoning, is handled by such large numbers of persons, and none is employed for such manifold and important purposes. Layet[1] made a list of 111 occupations in which industrial lead poisoning may more or less readily occur. He calculated moreover that the printers, painters, potters, and earthenware makers in and about Vienna, numbering in all about 44,380, furnished yearly at least 1563 cases of lead poisoning, with 43,045 sick days from this cause alone. Hayhurst states that in the Ohio potteries during 1914, 2585 workers were directly exposed to lead and that 109 were poisoned. Alice Hamilton's figures for the refining and smelting of lead state that, in 1912, 7500 employes contributed 1667 cases of lead poisoning, an incidence of 22 per 100. The census bureau of the United States in a survey covering two-thirds only of the mortality statistics in seven years (1910–1916) found 1085 deaths from plumbism. There were 13,000 cases of lead intoxication recorded in five years (Reily[2]). A marked reduction in incidence is general at present and there were only 246 cases of industrial lead poisoning in Great Britain in 1922.

The clinical interest is wide, for many of these industries furnish products that occasionally cause poisoning in those who use them. Accidental lead poisoning is much less important than industrial, and is less common now than formerly; but its sources are almost innumerable, some of them being evident, some most unexpected, and not a few dependent upon the use of lead in preparations which are of a secret nature and therefore more dangerous because the risk from them is often discovered only through the occurrence of poisoning. The clinical importance and complexity of the subject are largely increased by the fact that saturnism at times appears in most peculiar clinical guises, and the nature of the condition is extremely likely to be overlooked, particularly if a source of intoxication is not readily suggested by the history.

Etiology.—Race.—Racial susceptibility is not usually recognized; there are but few negroes employed in lead industries, Hamilton's[3] figures dealing with colored labor in lead smelting, intensifies the impression that the blacks are more likely to develop encephalopathies when poisoned.

Heredity.—That there is a family tendency to lead poisoning is claimed by various observers, particularly Oliver, who saw fatal saturnism in a father and four sons. Fetuses of animals poisoned with lead may have the metal in their tissues, and large amounts of lead may be found in the organs of a premature infant born of a mother chronically intoxicated with lead.

[1] *Poisons industriels*, Office du Travail, Paris, 1901.
[2] *Jour. Ind. Hygiene*, 1919, vol. 1.
[3] *Jour. Ind. Hygiene*, May, 1919, 1.

Age.—There are but few adolescents employed in lead industries in the United States; of the writer's 43 "trade" cases from the Toronto General Hospital only 11 were over forty years of age; Legge and Goadby insist that the young are twice as susceptible as adults to the effects of lead.

Sex.—Women are not employed in the heavier trades in this continent, nor do they work in white lead or commercial painting; pottery trade figures show that the incidence among the female employees is twice that of the male workers[1]; women are more subject also to the nervous and mental manifestations of lead poisoning.

Period of the Year.—It is generally recognized that workers in lead suffer more frequently during hot months. The especial frequency of accidental cases due to drinking-water during the summer and autumn has been repeatedly noted, and has been shown to be due to the especially acid nature of waters coming from peaty gathering grounds at these periods of the year.

Previous Diseases and Previous Attacks of Saturnism.—Any preëxisting disease that reduces the resistance, perhaps chronic renal trouble especially, increases the liability to attack. The tendency to further attacks, after once suffering from saturnism is very striking and is recorded in 16 of 43 cases in the Toronto General Hospital. This is usually due to further exposure, but Bernhard especially dwelt upon the fact that characteristic symptoms may appear without any renewal of exposure. Such instances are apparently due to the escape of lead into the circulation from the bones.

Habits.—Alcoholism is very important in increasing the liability to saturnism, and alcoholic excess frequently determines the actual onset of an attack, particularly of encephalopathy. Sexual excesses are insisted upon by Oliver as a predisposing factor, women of loose life suffering particularly. All depressing excesses, lack of exercise, and unhygienic habits, strongly favor poisoning; but the most important factor of all in a vast proportion of industrial cases is carelessness in inhaling dust or ingesting particles of lead. In most industrial poisonings, and therefore in the majority of all instances, the lead is actually breathed in or is ingested. Eating, drinking, using tobacco, or wiping the lips, without properly cleansing the hands are considered as contributing but slightly to the causation of lead poisoning.

Occupation.—This is overwhelmingly more important than any other factor and the occupations in which lead poisoning may occur are manifold; Hutton[2] tabulates 151. Some are naturally much more dangerous than others, the worst being those in which lead is freely handled and in which the exposure is most continuous, and particularly those in which there is much lead dust. In the average American white lead works, 30 out of every 100 workers are incapacitated each year, and 1 out of every 6 or 7 dippers in the potteries suffers in the same way.[3] Bauer[4] mentions the following as the most dangerous: lead mining and smelting; zinc

[1] Oliver: *Lead Poisoning*, 1914, p. 177.
[2] *Lead Poisoning, Provincial Board of Health, Ontario.*
[3] From the figures of Alice Hamilton.
[4] *Gesundheitsgefahrliche Industrien*, Kaup, 1903.

smelting; working in white lead and lead colors; making lead pipes and various other lead objects; making pottery and earthen-ware; type-setting and type-making; working in electric storage-battery factories; file-making; diamond-cutting and polishing gems and semiprecious stones; weaving, especially Jacquard weaving; making tinware; installing gas and water pipes. Of these, file-making and Jacquard weaving may be practically excluded in this country because of improved methods; type-setting seems to produce saturnism only rarely here, because improvements in mechanical methods have largely supplanted handwork; and apparently tinsmithing is not particularly dangerous at present, owing to improvements in soldering and general hygienic conditions. Installing gas and water pipes is certainly not a common cause, but it may be dangerous in large operations. The other occupations mentioned by Bauer are all dangerous here. Poisoning in miners occurs principally in carbonate mines, and not in those in which chiefly the sulphide is present, a fact that was formerly considered to be due to the relative insolubility of the sulphide. Carbonate mines are likely to be dry, and therefore more dust is produced in them, while sulphide mines are often wet; and the water in the latter usually contains sulphuric acid, which prevents formation of the carbonate from the sulphide. Careful investigation will always show that some cases of lead poisoning occur in the sulphide mines (Alice Hamilton) and as the practical experiments of Carlson and Woelfel[1] on a case of gastric fistula show that the sulphide is readily dissolved by gastric juice we can no longer exonerate the galena as a cause of poisoning. Legge and Goadby long made this same claim as a result of their early experiments. Smelting ores containing lead is dangerous, particularly when the ventilating apparatus is not perfect. Wholesale poisoning by the fumes from lead smelters has been classically described by Oliver in his treatise on lead poisoning.

Of all occupations the manufacture of white lead and of lead colors formerly furnished the greatest proportion of cases; but recent English statistics show that potteries, electric storage-battery works, plumbing and soldering and painting poison more than do the white-lead works.[2] The possible dangers in white-lead works before the advent of methods calculated to protect the workers were shown by Kaup's figures for the Bleiberg Lead-workers' Union in Klagenfurt. In 1894, the 45 members showed 61 attacks of lead poisoning (135.6 per 100), and the average per man, was 46.7 sick days in the year. In Herbert's works, in the same town, the attacks each year, per 100 workers, ranged from 13.2 to 24.6. The influence that has apparently been exerted by careful regulation of this industry in France is seen in the statement of Leclerc de Pulligny that although Paris and Lille are the centres for the production of white lead in France, the cases of the lead poisoning in the hospitals of Paris among those employed in this occupation numbered only 13 in two years. The English and German statistics are equally creditable and following the issuance of instructions by the Home office in 1912 the incidence of lead poisoning in the white-lead works was cut in half: it

[1] *Jour. Phar. and Exper. Ther.*, 1913–14, **5**, 549.

[2] Annual Report of the Chief Inspector of Factories, Great Britain, 1922.

may be added that in 1919 no case of poisoning by white lead was reported in Great Britain. Electric storage-battery factories are very dangerous, unless they are well conducted. At the Episcopal Hospital in Philadelphia there were 23 cases in the wards in a little over two years from one factory and many others in the out-patient department (Edsall).

Painters are common sufferers, and usually in inverse proportion to their cleanliness, intelligence, and skill. A considerable number of the skilled artisans, however, always suffer. In districts where lead is not smelted or manufactured and where no potteries exist, the painting trade furnishes the greatest number of cases: sand papering and burning off old paint are the most dangerous parts of the painter's trade.

Among others in some danger are the makers of rubber goods, particularly among the heavier kinds, and of glazed and enamelled metal ware; glaziers, ship-builders, sailors, laborers in structural iron works (handling freshly painted iron), Bessemer steel workers (Ormerod), workers in brass foundries and occasionally in other foundries, makers of the modern "secession" bric-a-brac, artist engravers, graphic artists; lace and passementerie makers, and workers in silk mills (when the silks are weighted with lead).[1] Poisoning among workers from lead dyes was once rather common; lead chromate is still used but is now of insignificant importance. In the Episcopal Hospital in Philadelphia, in the midst of vast textile industries, there were no industrial cases in women in a period of five years, and among 98 industrial cases in the men's ward in this time there was but a single weaver, and this man was probably poisoned from another source (Edsall).

In any obscure case the details of the patient's occupation should be investigated most minutely, for occupational sources of lead poisoning are multitudinous and often utterly unexpected.

Accidental Poisoning.—Detailed investigation is often necessary, both to determine the source and do away with it. Water is the most common source, though its frequency has been distinctly lessened by the reduction in the use of lead pipes for public and particularly for private supplies. Drinking-water becomes poisoned in a number of ways. The carbonic acid in rain- or spring-water may be the cause of poisoning, especially when new lead pipes are in use, soluble acid carbonate being formed; a deposit of relatively insoluble basic carbonate is gradually formed on old pipes, and acts as a partial but not absolute protective. Oliver states that distilled water will actively attack any lead vessel. A direct oxidizing or "erosive" action due to oxygen in solution in the water may take place. There may also be the formation of soluble salts of nitric, nitrous, or organic acids. Certain microörganisms may help increase the acidity of the water.

The almost epidemic poisoning of the Queensland children[2] was found to be due to ingestion of lead from painted woodwork of houses; Ruddock[3] reports 2 "pica" cases, children "paint gnawers;" ocular neuritis was a

[1] For conditions in Austria concerning this point see Kaup, *Gesundheitsgefahrliche Industrien*, etc., 1903, Fischer, Jena.

[2] Gibson: *Brit. Med. Jour.*, 1908, i, 1488.

[3] *Jour. Am. Med. Assn.*, May, 24, 1924.

prominent feature. Sleeping in freshly painted rooms has been held to be a cause of lead poisoning but the symptoms are probably due to the turpentine vapors.[1] Poisoning of women, practically epidemic, has been observed from washing the clothes of lead workers. Glazed earthenware and enamelled metallic vessels, used for cooking and preserving foods, have caused poisoning, though this is uncommon now with the better grades of such vessels. Formerly the lead in the solder or the tin made the eating of canned goods, or the use of tin vessels for acid foods, somewhat dangerous, but the risk is now minimal owing to improvements in the tin, the solder, and the methods of sealing; and the actual number of cases known to have been poisoned in this way, even in earlier years, is small. Lead is sometimes used in the making of drinking vessels and, in earlier times, caused many cases, especially when such vessels were used for cider, wine, or other acid beverages. Variot reported saturnism in a child from this cause. Children's toys, when made of lead, have caused poisoning, and the same may occur when they are colored with lead pigments, though the latter are probably used but little for this purpose. Candies were at one time colored with lead dyes, but this is rare at present; and the use of lead chromate in baker's products has hardly been heard of since Marshall showed how common it was in Philadelphia, and D. D. Stewart[2] reported a dangerous epidemic from this cause. Foods are so carefully watched that there is little danger from them directly. Soda water or carbonated water in siphons may cause poisoning, particularly if the tanks, siphons, etc., are made of lead; Cao found lead in carbonated water in siphons, and reported a series of poisonings due to this cause but there is little danger from this source in this country, as block tin and zinc have almost completely supplanted lead for this purpose. Cosmetics, hair dyes, and false teeth have been sources of poisoning. Severe poisoning from a face enamel is reported by Woltman.[3] Medicinal lead poisoning was known to the physicians of the ancients; it is generally thought to be uncommon now, but slight or moderate symptoms from this cause are probably not infrequent. The use of diachylon ointment over large eczematous surfaces is certainly dangerous, and has caused fatal poisoning in infants (Passler, Hahn, Holt[4]). Poisoning from internal use of diachylon as an abortifacient has been repeatedly observed in England (Ransom).

Infants have been poisoned by dusting powders containing lead, or by cosmetics or ointments used on the person of the nurse.

The duration of exposure before the development of plumbism has naturally varied greatly. Tanquerel repeatedly saw wrist-drop after a week's exposure, and others have had similar experiences. This is attributed to variations in individual susceptibility which may be extreme. Hobbs[5] in a very dusty white lead plant saw men sicken in from three days to less than two weeks; Hall speaks of flue-dust men showing symp-

[1] Herman: *Bull. Acad. Med. Belg.*, July, 1914, abstracted by Hutton.
[2] *Med. News*, December 31, 1887; and *Third Annual Report State Board of Health of Pennsylvania.*
[3] *Jour. Am. Med. Assn.*, November 11, 1923.
[4] *Am. Jour. Dis. Child.*, March, 1923.
[5] *New York Med. Jour.*, 1898, **67.**

toms in three days and being incapacitated in eight or nine days; a young painter, aged seventeen years (one of the Toronto General Hospital cases), developed colic, foot- and wrist-drop after six weeks exposure. A certain degree of immunity undoubtedly exists in some persons, others are certainly especially susceptible; intercurrent factors are known to increase or decrease susceptibility. Only in this way can one explain why workers, especially painters, have symptoms of poisoning after years at the same work: in one of the writer's cases a shift to sand-papering wheels was the precipitating cause after thirty years of immunity in painting.

Accidental or medicinal ingestion of single large doses has frequently caused somewhat prolonged poisoning, usually colic, though encephalopathy has repeatedly, and paralysis in rare instances, followed a single dose or a few doses. An interesting case of hematuria following the ingestion of lead acetate is given by Ockerblad[1]; 20 gr. of this salt in a period of two weeks produced bloody urine, colic and a lead line. Colic and indefinite symptoms of poisoning often occur soon after beginning work in lead. As a rule marked colic does not occur for several weeks or longer, and symptoms of poisoning may first appear after many years of exposure. Paralysis is usually a late development, commonly appearing only after preceding cachexia or colic, and therefore after prolonged exposure. Encephalopathy is not infrequently seen within a few weeks or months, but often arises late.

Pathology.—This is not characteristic. There is usually general emaciation; the blue line may be found. Arteriosclerosis is regularly found in the subjects of saturnism. Chronic gastro-enteritis is common, but no special changes have been described in the digestive tract except pigmentation of the walls of the intestine with lead sulphide and degeneration of the cells in the ganglia of the intestine. In experimental cases (Oliver) the intestine is often found in extreme spasm and the bloodvessels may appear as if in a state of vasoconstriction. A considerable number of observers have noted nephritis in the early stages and have produced it experimentally; one of the Toronto General Hospital cases gave the picture of acute glomerulonephritis. In old cases interstitial nephritis is a very usual lesion, often the most important. In a small proportion of cases the lesions of gout are present.

In cases with nervous lesions, the paralyzed muscles are more or less atrophic and show degeneration of the muscle cells and minute hemorrhage between the fibres. The peripheral nerves, whose territory was involved clinically, have always been found degenerated and have shown in addition small hemorrhages in the nerve sheath and between the fibrils. In the eye, vascular spasm and anemia can be seen as the cause of cases of acute transitory amaurosis; obliterative endarteritis, followed by swelling of the disk and atrophy of the nerve, is the lesion in permanent blindness. The motor cells of the anterior horns of the spinal cord show changes. Clumping or solution of the Nissl bodies is described; the cells themselves may even shrink and disappear. There is pleocytosis of the spinal fluid and there are changes in the meninges and white matter of

[1] *Jour. of Urology*, 1923, **10.**

the cord; peripheral neuronitis rather than perpheral neuritis is the condition present.[1] The usual gross cerebral lesions in encephalopathy have been œdema and anemia, flattening of the convolutions, thickening of the pia, and small hemorrhages. Microscopic studies show marked changes of the cortical cells, hemorrhages, and proliferation of the cell nuclei in the vessel walls and of the glia cells about the vessels. The lesions although resembling those of acute encephalitis macroscopically are essentially different histologically.

Mode of Entrance and Pathogenesis.—There are three common channels of entrance: the *respiratory*, *gastro-intestinal*, and *cutaneous*.

The conditions of anthracosis and pneumokoniosis should have made us realize that lead dust could easily reach the lungs and be there absorbed; the occurrence of many cases of colic in the mining and smelting industries shows that lead fumes are capable of causing poisoning. On the other hand a large part of any dust which reaches the nose or mouth is swallowed with the secretions, and Lehman, Saito and Majima say that of inhaled dust 12 per cent. reaches the lungs and 70 per cent. the alimentary system. The most convincing observation is that of Blumgart[2] in tying off the œsophagus, and spraying lead into the nares or trachea; he produced poisoning at once and with only a fraction of the amount of lead, which took weeks to poison the animal, when given by the alimentary tract. Prevention of dust and removal of fumes, by exhausts, in the handling of powdered or fuming preparations of lead are followed at once by a diminution in the number of cases of plumbism. "A lead salt is poisonous in direct proportion to its dustiness."

Small amounts of lead are doubtless constantly ingested by lead workers; the water-borne epidemics and cases following the administration of lead give the most unquestioned examples of gastro-intestinal origin; in the empty stomach, lead chloride is probably formed, which lower down is easily absorbed. On the other hand, the mixture of food and ingested lead results, in part at least, in the formation of insoluble peptonates and albuminates.

The skin probably admits but little lead into the system; cases of lead poisoning have followed the continued use of hair dyes and lead plasters, according to Süssman[3] lead in an oil base is absorbed in some quantity. It is not now considered that absorption through the skin of the hands affects the radial nerves directly.

The greatest amount of lead is found in the skeleton. Only minute quantities are found in the kidneys; the brain, cord, nerves, muscles, bones, and other tissues contain various amounts. In many instances the brain contains little or no demonstrable lead, even in encephalopathic cases. Hard bone is the great store-house for lead in the system and may hold it for years.[4]

The manner in which lead acts is in many points still a subject of

[1] Hyslop and Kraus: *Arch. Neurology and Psychiatry*, October, 1923.
[2] *Jour. Am. Med. Assn.*, August 23, 1924 and *Lead Studies VI*, *Jour. Indust. Hyg.*, September 5, 1923.
[3] *Munchen. Med. Wchnschr.*, 1918, **65.**
[4] Minot: *Lead Studies V*, *Jour. Indust. Hyg.*, 1924, **6.**

controversy. Colic seems to be due to spasm of the bowel, dependent most probably, but not certainly, upon changes in the intestinal ganglia. The changes in the muscles, together with the peculiar localization of the paralysis and the absence of sensory symptoms, suggests that the paralysis is spinal in origin. It seems probable (Edinger, Teleky) that the peculiar distribution of lead paralysis, represents a "playing out" or exhaustion of those nerves and muscles most called upon in the performance of the various movements required in the different trades or activities; painters get wrist-drop early, file-makers show atrophy of the interossei, workers in the trades requiring heavy lifting are more apt to show affection of the shoulder muscles. Most studies dwell upon the occurrence of marked inflammatory degeneration in the minute arteries, leading to rupture of their coats and hemorrhagic infiltration of surrounding tissues.

A small amount of lead is excreted through the kidneys and it is partially excreted in the feces; as much as 2 mg. per day may pass in this way and yet the subject be not considered in danger; much of the ingested lead therefore is not absorbed or goes into the liver and out again. A little excretion occurs through the sweat, but this is of slight importance. It has been found in woman's milk (Bulland), a fact of interest in relation to the infants of lead-poisoned women. Hall's reports on the Aguas Callientes cases show that the placentas of "leaded" pregnant women regularly contain lead. Lead has been demonstrated in the parotid glands and saliva. The minimum dose capable of producing poisoning when long-continued is difficult to determine. Teleky and Brouardel considered that 1 mg. daily as a dose for several months may suffice to cause symptoms; 10 mg. will produce a severe intoxication.

Symptoms.—The clinical course of plumbism consists, in most instances, of the development of more or less marked but indefinite general symptoms, followed after a variable time, usually at least several weeks, by the appearance of *colic*. Less commonly, but still frequently, paralysis supervenes; occasionally the graver cerebral manifestations occur, usually after some previous colic. There is no constancy in the course of the symptoms; violent colic may be the first manifestation soon after exposure; paralysis may develop very early; and in rare cases, without preceding noteworthy symptoms, coma, or an outburst of convulsions or of more or less dangerous delirium, may be the first recognized evidence of poisoning; occasionally indefinite ill health without distinctive symptoms lasts for years and ultimately causes death, with the picture of cardiovascular-renal disease.

It is important to recognize that preceding *general symptoms* are practically always present. The earliest manifestations of these are from the blood and vascular system. A curious sallow pallor, with a marked wasting of the subcutaneous fat and a slight actual anemia, gives the picture of lead cachexia. Loss of appetite, gastric distress, a metallic taste, furred tongue, offensive breath, with constipation or diarrhœa, are frequent, early, general symptoms of an affected digestive system. Insomnia, restlessness, mental and physical depression and weakness, are common nervous symptoms preceding the severer later

conditions. There may be a slight rise in blood-pressure, but this is not as a rule distinctly in evidence unless an estimation is made during periods of colic. Pains in the limbs and body, pains in nerve trunks and joints, weakness of the muscles to be later paralyzed, are other fairly constant early signs. At any time the more distinctive characteristics of lead poisoning, colic, paralysis, or cerebral symptoms, may appear with the general symptoms. Colic almost always develops and usually soon after the first signs of ill health. It was recorded in 32 of 43 cases from the Toronto General Hospital records; in young children the history of an early colic is often lacking, and there is an impression on the part of most observers that the nervous manifestations predominate in cases of poisoning in the very young. Paralysis, when it occurs, commonly comes on after some cachexia has appeared; that is, after poisoning has lasted for a considerable period. Encephalopathies may develop early if the poisoning has been severe, but they likewise may occur later.

Two conditions, *basophilia* of the red blood cells and a *blue line* on the gums, are at times present in the early stages of absorption of lead, and often when there are no actual symptoms of intoxication. Basophilia is more a finding in the acute forms of lead poisoning; it was practically absent in the blood of Hayhurst's series of 100 painters, 73 of whom had or had had signs of chronic intoxication. The opinion of many competent observers is, that basophilia is not invariably present in the lead poisoning. It may appear when exposure has been extremely brief; White and Pepper[1] found it after four days of industrial exposure and after a single dose of $7\frac{1}{2}$ gr. of lead acetate, basophilia was evident in twenty-five hours. The experimental work of Keys[2] shows that when anemia has been first produced by bleeding, that the subsequent absorption of lead is regularly followed by diffuse stippling and basophilia, most intense in the early days. Basophilic cells are polychromatophilic, reticulated, and stippled; they are young red cells. Studies on the effects of lead on red blood cells by Aub, Reznikoff and Smith[3] suggest that lead forms an insoluble lead phosphate in the cell, which shrinks, becomes brittle and resistant to saline below normal strength. Trauma and breaking up in the capillaries, rather than hemolysis, is the cause of anemia. No definite relationship of basophilia to the degree of anemia can be shown, although the reaction that produces the basophilia will in the end produce anemia. In the Toronto General Hospital records basophilia is recorded with hemoglobin of 80 to 90 per cent. and red cell counts of 4,000,000 and over. Basophilia is shown by the mixed shade of the cell when stained with eosin and methylene blue or with the usual blood stains, by the reticulum as shown by the so-called reticular stains and by the stippling with fine or coarse granules of blue in the various methylene blue stains of which Manson's is perhaps the best. In many other conditions associated with blood alteration or destruction a basophilia may be found and the changes are not specific to lead. Associated with a suspicious history and sug-

[1] Contributions from the William Pepper Laboratory of Clinical Medicine, 1901.

[2] *Lead Studies, Blood Changes in Lead Poisoning in Rabbits, Am. Jour. of Phys.*, 1924, **70**, No. 1.

[3] *Jour. Exper. Med.*, August 1, 1924.

gestive signs of lead absorption the occurrence of basophilia has great confirmative value, and is to be considered as a reaction in the cells themselves.

The *blue line*, sometimes called Burton's line, was first studied clinically by Burton in 1834, and practically at the same time by Tanquerel. It appears as an irregularly linear or broader, dark blue discoloration of the margin of the gum. Close inspection shows that it is frequently a line's breadth from the edge of the gum, though if the latter is loosened and overhanging or is atrophied, the line is often on the very edge. It may appear stippled to the naked eye, and a hand-lens shows that it is made up of fine, nearly round dots, sometimes discrete, sometimes closely clumped together. At times it consists of a few isolated dots or of a very slight and ill-defined line, especially if the gums and teeth are in good condition. It is not usually continuous from one tooth over to the next; the portion of the gum situated between the teeth shows it most commonly but little separate arches, or partial arches, may form over the bases of the individual teeth. It is especially marked about the incisors and canines, and particularly in the lower jaw. This line is due to deposits of lead sulphide in and about the epithelial cells, already swollen and loosened as a result of gingivitis.

With the basophilia and blue line there may early be some secondary anemia, but the counts rarely show the red cells below 2,000,000. There is some reduction of the hemoglobin; usually not severe and rather more than proportionate to the decrease in red cells. Nucleated red cells are frequently present in small numbers. The anemia is often more apparent than real and the pallor, like that of arteriosclerosis, may be due to vascular spasm.

Poikilocytes, microcytes and megalocytes may appear and may suggest the diagnosis of pernicious anemia. There were no counts below 3,000,000 in the Toronto General Hospital cases; hemoglobin percentages of 50 and 40 are recorded with red cell counts of over 4,000,000; no evidence of a real mononucleosis or polynucleosis was seen.

When actual symptoms of poisoning appear they are both general and local. Slight fever (99.5° to 100° F.) is present in unusual cases, and at times may be somewhat prolonged; this may cause confusion in diagnosis. The most important local effects are as follows:

Digestive Tract.—Anorexia, an unpleasant sweet or metallic taste, furred tongue and offensive breath, are frequently complained of in the beginning, and the last symptom is often extreme in well-developed poisoning. Nausea and vomiting are very common (Tanquerel, Stewart); Oliver noted attacks of epigastric pain which may be violent. Constipation is the rule and is frequently extremely obstinate, especially when colic has developed; occasionally constipation alternates with diarrhœa, and rarely there is persistent diarrhœa. Among rarer disorders of the digestive tract are salivation, severe stomatitis, parotitis, and ulcerative colitis.

Colic is the chief symptom referable to the digestive tract. It is not due to disturbed digestion, but apparently to spasm of the bowel of nervous origin. In severe accidental poisoning, colic may appear after a

single dose, and occasionally in industrial poisoning within a few days. Usually weeks or months of poisoning and frequently similar periods of indefinite ill health precede it. Generally the patient has been constipated beforehand, often severely so, and commonly forebodings of pain have already been felt when the first attack of actual colic comes on. Severe pain then appears, often in the night, generally below the umbilicus, in frequent paroxysms lasting for a few seconds or minutes, in some cases even for hours. The severity of the pain varies; at times it is extreme, and the patient is cold, pallid, sweating, and almost collapsed from suffering, with a small pulse of high tension and remarkably slow. The abdominal walls are usually hard and retracted during the paroxysm and pressure upon them gives relief. Vomiting is common during the paroxysm and constipation is usually most obstinate until the spasm of the bowel is over. Frequent endeavors to defecate result only in the expelling of a little mucus. The secretion of urine is much reduced. The duration of an attack, with the paroxysms and remissions, is sometimes a few hours only, more commonly several days, frequently ten days or a fortnight. The severity usually decreases continuously after the first day or two of treatment. Recurrences are the rule if exposure continues; they occasionally develop long after exposure has ceased.

Respiratory Tract.—Aphonia and dyspnœa from laryngeal paralysis have occurred. Asthma is an occasional though uncommon result of the intoxication. Pulmonary tuberculosis is unduly common in subjects of plumbism, partly as a result of inhalation of irritants, partly from reduced general resistance. Printers and type-setters seem particularly liable to this form of infection according to German, French and Austrian figures, in American this is not so apparent.[1]

Cardiovascular System.—Arteriosclerosis is common in lead-workers even at an early age. Ronnberg, the statistician of the Chicago Painters union, states that one-quarter of those poisoned for a long time ultimately exhibit the symptoms of cardiovascular incompetency, and die from circulatory failure, or occasionally from cerebral accidents. High blood-pressure was not a feature of the Toronto General Hospital cases, figures of 160 systolic and 110 diastolic were the highest recorded; systolic pressures of 105 and 112, and diastolic of 75 and 60, were seen after six and seven years of symptoms.

Genito-urinary System.—A slight degree of albuminuria with some casts is not uncommon in the early stages, especially if the dosage has been large. Albumin and casts are frequently present during an attack of colic. After prolonged poisoning, progressive chronic renal changes may become the most important feature of the case, yet it is rare to have lead-workers leave their occupation with outspoken kidney signs or symptoms. Suppression of urine, spasm of the bladder and urethra, and sometimes retention of urine, may be seen with colic. The influence upon the generative organs is seen chiefly in women, though the progeny of leaded males is said to be of lessened viability and Hayhurst's figures indicate that the chronically poisoned father begets few children. Menstruation becomes

[1] Hamilton: *Hygiene of the Printer's Trade, U. S. Dep't. of Labor: Bureau of Labor Statistics,*

disturbed, being usually excessive and irregular; and pregnant women with saturnism are extremely likely to abort or to have premature labor.[1] In the latter case the child is often stillborn, or it is very frail and usually soon dies. After exposure has ceased, women often pass through repeated normal labors.

Arthritis.—Gout occasionally occurs, but it seems that other predisposing causes are necessary in addition to plumbism. None of the Toronto General Hospital cases showed arthritis. Goadby notes that gout when seen in connection with lead-workers is usually in those who work with paints, and suggests turpentine as the cause of the gouty manifestation. Saturnine gout is apparently somewhat peculiar in that it involves joints ordinarily spared; Hayhurst however noted the involvement of the toe-joints alone in 8 of 100 painters.

Nervous System.—Moderate pain, often indefinitely located, is common in both the extremities and the trunk, especially in early stages. Minute hemorrhages in the nerves are the probable cause of these neuralgic pains. Pains in the joints appear in intermitting paroxysms, which may be very severe and last for days. They are usually most marked in the knees or ankles. The muscles sometimes ache severely, and may be tender, especially those that are soon to become paralyzed. Other sensory symptoms are usually slight. They may be paresthesias, and general sensation may be reduced or lost over the back of the forearm, less commonly over the front of the leg or other localized area. Hyperalgesia is occasionally noted, and in rare instances there is much tenderness over the nerve trunks. Sometimes actual hysterical symptoms are present with hemianesthesia or other characteristic stigmatic local areas of anesthesia. Cerebral accidents (hemorrhage, etc.), if they occur, may produce hemianesthesia.

With the diffuse pains, certain muscles, particularly those of the calves, may go into mild or severe cramp. This seems to be particularly the case in children (Turner). Fibrillary twitching of the affected muscles is common after paralysis has developed. Tremor is frequently noted, especially in old cases. It affects chiefly the hands, and is usually of slight amplitude and not striking, though it is sometimes coarse and may resemble the tremor of paralysis agitans.

Most important of all the nervous symptoms is paralysis; in its usual distribution it is of itself almost distinctive of lead poisoning. The lower muscles supplied by the seventh and eighth cervical and the first thoracic segments are most affected. A typical paralysis produces bilateral "wrist-drop," and "toe-drop." There is at first an increasing degree of weakness in the extension of the fingers at the metacarpophalangeal joint (paralysis of the extensor communis digitorum), followed by weakness and often complete paralysis of the extensors of the wrist. Palsy often begins in one hand, the other following within a fortnight or less; frequently the hand first involved has been subjected to special strain. The paralysis is usually subacute in its onset, reaching a marked degree within from a few days to a fortnight; occasionally it progresses very

[1] Oliver: *Lead Poisoning*, 1914, p. 181.

slowly. In "wrist-drop," the "antibrachial" type of paralysis, the hand is in flexion at the wrist from paralysis of the extensors, with unopposed action of the flexors, and the fingers are similarly moderately flexed, owing to paralysis of their long extensor. At first, the distal phalanges can be extended if the proximal phalanages be first passively extended, for the interossei, the proper extensors of the distal joints, are as yet uninvolved; the thumb muscles, the extensor indicis, and extensor minimi digiti also usually functionate at first. Later, these extensors, the interossei, and the muscles of the thumb are affected; capsule polishers may show the thumb extensors early involved; distal extension of the fingers and extension and adduction of the thumb are imperfectly performed, or impossible. The long abductor of the thumb often becomes involved late, but in early stages is usually spared; and the supinator longus is almost never included in this common type of paralysis, a point of great importance because it opens the question as to the situation of the lesion in lead paralysis. This sparing of the supinator fibres, while the rest of the nerve is involved, is certainly against the idea of a purely peripheral affection. The distinctive characteristics of this anti-brachial or lower arm type are, that it is almost always bilateral, is purely extensor, spares the long supinator and usually the long abductor of the thumb, and there are rarely any sensory symptoms, except, perhaps, limited cutaneous anesthesia over the backs of the forearms. Atrophy begins soon in the affected muscles, especially those of the back of the forearm; marked reduction or loss of response to the faradic current appears; and there develops the reactions of degeneration. As a rule, some of the muscles other than those distinctly paralyzed are weak, and may even show the reaction of degeneration. The paralysis ordinarily soon reaches the limit of its intensity and extent. Fresh cases quickly improve within a few weeks after proper treatment is begun, and generally recover almost completely within a few months if they are not extremely severe. In older cases recovery is slow, and dependent upon the grade of the palsy and its duration: if long neglected and severe, complete recovery is not common, and occasionally very little improvement occurs.

This latter type of case, with persisting flaccid paralysis, intensifies the suggestion that the whole lower neuron is at times affected with destruction of the anterior horn cells. Hyslop and Kraus[1] give an excellent account of the opinions on this question; most observers have departed from the idea that lead paralysis is merely an expression of peripheral neuritis.

Forms of paralysis other than characteristic wrist-drop may occur. The Aran-Duchenne type is occasionally seen; in it the small muscles of the hand, the interossei, and the thenar and the hypothenar early become atrophied and more or less paralyzed, and these changes produce the "simian" hand. This is not a clearly individualized type in lead poisoning, being usually associated with the previously described form. The Aran-Duchenne form has been particularly noted in persons whose occupation, such as file-making, causes a special strain on the small

[1] *Arch. of Neurol and Psych.*, October, 1923.

muscles of the hand. Goadby states that file-cutters show by far the greatest incidence of paralysis. The upper arm, the brachial, or Duchenne-Erb type, in which the deltoid, often the biceps and the brachialis anticus, and sometimes the supra- and infraspinati, are involved, occurs occasionally, particularly in those whose work requires heavy lifting. In it the arms hang by the side, rotated somewhat outward and incapable of abduction, and in severe cases incapable of flexion at the elbow. This form has repeatedly been seen as a separate condition, though it is usually associated with paralysis of the extensors of the fingers and wrist. Contrary to the conditions in the ordinary forearm type, the supinator longus is likely to be involved in this variety and the picture of deltoid-biceps supinator paralysis is seen, practically a segmental involvement, and highly suggestive of a central spinal affection. Of this group of muscles, the deltoid is especially liable to paralysis, and it has repeatedly been the sole muscle palsied; sometimes it has been paralyzed on one side only.

The lower limbs are infrequently affected in adults, and, when they are, the arms usually suffer also; the conditions in children differ markedly in this point. In the legs, the peronei and the extensor of the toes are the typical seat of paralysis, the tibialis anticus, like the supinator longus in the arm, almost always being spared. In rare instances in adults, more commonly in children, the tibialis anticus is paralyzed in association with the gastrocnemii, while the muscles usually affected escape. The disease, in the legs, as in the arms, is practically always bilateral. The small muscles of the feet occasionally show special involvement. Rarely the disease is situated chiefly in the muscles of the thigh. The knee-jerk may be increased when the legs are affected; it may be normal, since the quadratus femoris is not usually affected; sometimes it is reduced or lost.

Paralysis of the cranial nerves is occasionally noted. The nerve most frequently involved is the optic, though fortunately this is rare. No case of optic neuritis or optic atrophy due to lead has been recorded in the Toronto General Hospital in ten years. Laryngeal paralysis has been described from the days of Tanquerel who noted its occurrence also in horses employed in lead works. The paralysis most commonly affects the adductors and causes hoarseness or aphonia, though the abductors have repeatedly been paralyzed and produced marked inspiratory dyspnœa. The facial nerve has been paralyzed. Other cranial nerves, separately paralyzed as the result of lead, are the abducens and the oculomotor; paralysis of these nerves, as of the optic, is commonly associated with cerebral signs. Sometimes several ocular and other cranial nerves have been involved coincidently. Ophthalmoplegia, complete with the exception of the superior oblique, is described by Gibson.

In addition to the localized forms of paralysis, cases are occasionally seen in which generalized paralysis appears, usually advancing from the periphery toward the trunk. In these instances it is probable that both spinal and peripheral changes are present. There are two important varieties: one acute, the other progressing slowly. Fever may accompany the acute form. Both ordinarily end in recovery but rarely death has occurred from asphyxia. In rare instances, paralysis of the diaphragm

has occurred, even without general palsy. A few cases have been seen of multiple paralysis resembling a type of progressive muscular atrophy. Some cases have been observed in which conspicuous ataxia, absent knee-jerks, and very slight paralysis, produced some resemblance to locomotor ataxia. Putnam, Bechtold, and Oppenheim report cases resembling spastic spinal palsy, with the presence of lead in the urine. Cases with the clinical signs of amyotrophic lateral sclerosis have been produced by lead poisoning and with definite changes in the spinal fluid one is compelled to assume the existence of spinal cord changes.

Cerebral Symptoms.—*Encephalopathy.*—Transitory hemiplegia, aphasia and choreiform movements have been occasionally seen. There may be hysterical symptoms, "toxic hysteria," with hemianesthesias and other stigmata, or hysterical outbreaks of excitement or convulsions, especially in predisposed young women. Late in the course of old cases, nephritis and arteriosclerosis may cause apoplexy, with persistent hemiplegia or other cerebral lesions.

The most common and striking cerebral symptoms are psychic depression, epileptiform convulsions, mania, delirium, and coma; sometimes a picture more or less closely resembling paretic dementia. In Tanquerel's 1217 cases, encephalopathy occurred 72 times. Its frequency varies according to the dose, and perhaps, according to the nature of the lead compound ingested. In Stewart's chrome-bun series of 64 cases, encephalopathy occurred 15 times. These latter figures are, however, perhaps partly due to the fact that many children were affected. Hamilton[1] found 16 encephalopathies in 144 cases of pottery lead poisoning, the woman workers contributing by far the greater number of cases, no less than 1 in 4 showing brain symptoms. The outbreak often comes suddenly; alcoholics are especially liable. Convulsions, or less commonly delirium, usually occur first. Coma may follow. The convulsive attacks are epileptiform with clonic and tonic movements; only one may occur, but, as a rule, the attacks are repeated at varying intervals over days—rarely, even weeks. Epileptiform attacks have occasionally persisted. In the delirious form the patient may be very violent; convulsions not uncommonly interrupt the delirium, and there are often striking changes from violent intellectual and motor activity to hebetude and quiet. Delusions of persecution and particularly hallucinations, especially of terrifying character, are common; though they are not confined to such subjects, hallucinations are very frequent in those who are also alcoholic, and with marked tremor the resemblance to delirium tremens may be striking. Fever (100° to 101°, occasionally even higher) is not uncommon. The duration may be extremely brief, but more commonly delirium lasts from several days to a fortnight or sometimes longer; in unusual instances the patient remains insane. Robert Jones, Savage, and Goodall claim that in institutions there are a definite number of patients whose insanity has been produced by lead intoxication. The fact that delirium may be of sudden and violent onset is at times one of grave moment. Acute encephalopathies are very dangerous; 30 to 35 per cent. of all "lead deaths" are

[1] *Lead Poisoning in American Industry, Jour. Indust. Hyg.*, May, 1919.

associated with brain involvement (Goadby). Tanquerel saw 16 deaths in 72 cases, and as a rule the mortality is put higher than this. Death usually occurs in convulsions, in coma, or from general exhaustion.

Symptoms of general paresis have been observed in a considerable number of cases. The onset is, however, more rapid and speech is less disturbed than in ordinary paretic dementia, moral vagaries are less common, and recovery often occurs even from extreme states.

Eye Symptoms.—Disease of the external ocular nerves produces the corresponding muscular paralyses. Nystagmus has been observed. Hemianopsia, usually homonymous, may appear rarely. Transitory blindness may develop suddenly, usually in encephalopathic cases; this blindness commonly disappears rapidly and completely and is probably due to vascular spasm or to hemorrhage. Vision may gradually become impaired, with the symptoms common in other forms of amaurosis, and, of these, probably at least one-half show persistent structural changes in the optic nerve (deSchweinitz). Ophthalmoscopically, the transitory cases may show nothing; the changes in other cases are those common in amaurosis, except that lead subjects show especially marked vascular lesions; and it is also noteworthy that in optic neuritis the lesions are not confined to the parenchyma, as in the nerves of the extremities, but are also interstitial and perineuritic. The picture of a severe albuminuric retinitis may be produced with great swelling of the disks; diffuse neuroretinitis was a common finding in the eyes of affected children (Gibson). Serious eye symptoms are fortunately rare in this country; de Schweinitz saw only 3 instances in over 15,000 eye cases. Blindness and failing vision without fundus changes have been described; such cases are due probably to retrobulbar or central changes.

Lead Poisoning in Children.—Plumbism in infancy and early childhood commonly shows some clinical divergence from that in adults, and a brief mention of it is demanded. It is, naturally, not common in the very young, since it is always accidental in them.

Symptoms.—It is possible that some of the sickly, nursing infants of mothers with plumbism have lead poisoning and die of it. Infants seem prone to convulsions when poisoned by lead. Colic, pains in the legs, and cramps in the muscles are common. In older children there is a striking frequency of cerebral symptoms, such as convulsions, retraction of the head, and rigidity of the neck. Meningitis is often suspected, and Turner and Gibson refer to the marked frequency of ocular paralyses and optic neuritis. In paralysis in children the legs are almost regularly affected; a further peculiarity, as compared with adults, is noted by Turner, the peroneal muscles usually affected in adults often escape, while the tibialis anticus is usually paralyzed.

Ocular Symptoms.—Paralysis of the abducens and the oculomotor nerves, ophthalmoplegia and blindness are often observed; sometimes the latter disappears, and sometimes it becomes permanent from progressive optic atrophy. Gibson's term "ocular neuritis," is expressive.

Tetra-ethyl-lead.—Sensational accounts of poisoning by this compound appeared in the press in the autumn of 1924. Tetra-ethyl-lead had been introduced into gasoline to prevent carbonizing in the cylinder and on

the piston head of gasoline engines. Forty men at one plant sickened and showed signs of acute insanity; 5 of them died. Cases were reported from several places. Gilman Thompson, under whose observation many of the patients came, states that the chief menace is from the rapid absorption by the skin; he considers the symptoms as unique and as having no resemblance to those of chronic lead poisoning. The danger did not come from the exhausts of the motors but from the handling of the substance itself and from the fumes encountered in mixing it with gasoline. Thompson further states that lead, as lead, is found in the brains of animals poisoned by the application of tetra-ethyl-lead to the skin. Gettler analyzed the tissues and he also leans to the opinion that the symptoms are not those of uncomplicated lead poisoning. He considers that the substance is so decomposed in the tissues that only the lead will be found on examination; he was able to isolate some tetra-ethyl-lead from the brain. Seven and one-half grains of lead were found in the brain of one of the bodies autopsied. It would seem therefore that the lead itself may be responsible for some of the symptoms. The subject is discussed by Hamilton, *et al*[1], and the report of Eldridge and of the U. S. Bureau of Mines is considered. A critical review of the U. S. Bureau findings is made by Drinker and Edsall.[2] Eldridge speaks of the intoxications and symptoms as acute lead poisoning; Drinker and Edsall are of the opinion that chronic poisoning from the lead chloride and bromide in the exhaust gases is a distinct possibility.

Diagnosis.—Proper knowledge of the sources of lead poisoning, and alert attention to details in the history indicative of exposure, will often give an immediate suggestion of the nature of the case, even when the symptoms are unusual. The early diagnosis of lead poisoning is well considered by Lilienthal in Kober and Hanson's text-book; pains in the joints and bones with tremor and nervousness and ill health may constitute the picture of chronic poisoning. Cachexia, colic, wrist-drop, and toe-drop are the most common results of lead absorption and, when characteristic, are sufficient for the diagnosis. Their association with a clear source of poisoning, and especially with a blue line, makes the diagnosis practically certain. The absence of a known source of lead is not of much diagnostic importance if the signs are definite; and, even if the blue line is absent, bilateral wrist-drop without involvement of the supinator longus, and with no affection of the flexors and no noteworthy sensory symptoms, is nearly decisive, though to be completely so it needs confirmation through finding lead in the urine. The search for lead should be undertaken early and after giving potassium iodide or acids for a few days. The slight and fragmentary forms of the blue line, which may require a lens to determine their nature accurately, should be carefully sought when a more characteristic line is absent. Basic granulation that is very marked (with hematoxylin-eosin, thionin or Manson's methylene blue stain), and that is not associated with profound changes of other kinds in the blood cells or with some distinct cause, such as malaria or blood disease, is suggestive and may lead to a correct diagnosis. The

[1] *Jour. Am. Med. Assn.*, 1925, **84**, 1481.
[2] *Jour. Indust. Hygiene*, 1925, 7.

basophilic aggregation test as described by McCord, Minster and Rehm[1] should be applied in all suspected cases; this test is based upon the fact that young cells, the stippled cells, tend to cohere in thick specimens; staining after hemolyzing will show aggregations of stippled cells.

Cerebral cases and the slight or more unusual forms of paralysis are much more likely to be misinterpreted. General paresis, epilepsy, any toxic mania, coma, or delirium may be suspected. In children showing "ocular neuritis" and retraction of the head, with stiffness of the neck, meningitis may be diagnosed (Gibson); poliomyelitis, tabes, spastic paraplegia, and muscular dystrophies may be acutely simulated. When convulsions or eye symptoms are present the possibility of uremia must be considered. If the cases are of industrial origin, attention to the occupation usually suggests the diagnosis, and a search for the blue line, for basic granulation and evidences of cachexia may furnish more direct evidence. It is to be remembered, however, that none of the latter signs constitutes final evidence that unusual varieties of paralysis are due to lead, and if distinctive symptoms are absent, or a source of poisoning is not known, recourse must always be had to examination of the urine; and in any doubtful case the diagnosis must depend upon this. The chief source of error in the blue line is in the fact that it may persist for years after lead poisoning has disappeared, the lead coming from the storehouse in the bones (Minot), and it may, therefore, be present with other conditions that have developed later.

In cases with only general symptoms the finding of lead in the urine is the sole reliable source of diagnosis. Many methods have been devised for the purpose of finding lead in the excreta and tissues, most of which have proved unsatisfactory, since organic material may mask the presence of lead. Minot[2] admits that the electrolytic procedures have definite sources of error when applied to organic matter such as urine, feces and tissues; manganese and copper, more or less normal constituents of feces, make the electrolytic methods distinctly unreliable—Fairhall's chromate process seems more trustworthy; he gives a complete résumé of the subject and his papers should be consulted.

Prognosis.—General disorders that have not caused serious organic lesions, colic, and the mild and recent palsies, recover entirely under proper treatment. The older and more severe forms of paralysis have a prognosis as to complete recovery that is directly related to their duration and intensity, severe protracted cases rarely showing complete recovery. Persistent atrophy and progressive decrease or entire loss of response to electricity are bad signs and suggest anterior-horn-cell involvement. Cerebral symptoms are always dangerous, coma particularly so; if, however, the patient escapes death from encephalopathy, serious consequences rarely follow. Eye symptoms, especially of slow onset, are of very doubtful prognosis. About half of them have persistent optic atrophy, and this goes on to blindness in a large proportion of cases.

[1] *Jour. Am. Med. Assn.*, May 31, 1924.

[2] Dennis and Minot: *Jour. Biol. Chem.*, 1919, **38**, 45 and Minot: *Critical Note on the Electrolytic Determination of Lead in Biological Material*, *Jour. Biol. Chem.*, January, 1923. Fairhall: *Estimation of Minute Amounts of Lead in Biological Material*, *Jour. Indust. Hyg.*, May, 1922.

The prognosis as to future attacks depends almost entirely upon the discovery and exclusion of the source of poisoning, renewed outbreaks from old lead deposits in the body being very unusual. If the exposure continues, recurrences are probable and are of worse prognosis than the original attacks.

In renal, cardiovascular, and other changes resulting from lead poisoning, the prognosis is dependent upon the severity and stage of these lesions. If the further absorption of lead is stopped, the progress of the lesions that have resulted is, of course, slower.

Prophylaxis.—Were the industries that cause exposure subjected to reasonable regulations actually enforced, and were the workmen given opportunity to keep themselves clean, and required to do so, industrial lead poisoning would largely disappear. The effect of enforcement can be seen in the results in Great Britain where cases of lead poisoning have dropped from 1056 in 1900 to 247 in 1922: in the pottery trades the incidence is now but one-fifth of that of twenty years ago, in white lead one-fifteenth.

Prevention of *dust-inhalation* is the most important part in prophylaxis, and the most difficult to carry out, owing to the carelessness of most workmen and indifference on the part of employers. Much is due to a lack of proper comprehension of the dangers and the methods of avoiding them. The regulations in a number of European countries[1] are examples of what should be done. In Belgium, white lead intended for paint-work may not be sold, transported or used except in the form of a paste combined with oil and dry scraping or dry pumice stoning of white lead surfaces is prohibited; some of the Swiss Cantons do not permit the use of lead paints; since 1915 France has dispensed with white lead as a painting base. The regulations in England, Germany and Austria are equally comprehensive, though varying in the nature of the prohibitions. England permits the use of white lead under strict supervision; no such governmental supervision exists in the United States. Important among these regulations are those that demand certain forms of ventilation, height of ceiling, isolation of the most dangerous parts of the work from the other portions of the plant, apparatus for the exclusion of dust or for the removal of that which escapes into the atmosphere, daily cleansing, and such construction of the walls and floors as to permit of easy and thorough cleaning, the provision of separate eating-rooms and of free baths, the exclusion of women and children from the dangerous parts of the work, limitation of the hours of work and of continuous exposure of the same individuals to the most dangerous parts of the work, and the services of a physician who has power to "lay off" any suspicious cases from work and who must report them. In some countries it is required of the workmen that they change their clothes and bathe after working, wear gloves or rub their hands with grease when at work, and do not eat, drink alcoholic beverages, or smoke or chew tobacco in the

[1] See *Gesundheitsgefahrliche Industrien;* Firgau, *Gifte und Stark Wirkende Arzneimittel,* Haering, Berlin, 1901 (German laws, etc.); *Poisons industriels; Dangerous Trades,* ed. by Oliver. Hutton's compilation for the Province of Ontario gives in full the regulations in various countries.

work-rooms. The enforcement of these laws is sometimes unfortunately lax and unless the question of dust and fume inhalation is given most consideration the laws may be labelled as almost worthless.

Of the simpler preventive measures, proper cleansing is by far the most important. Respirators are of little use because the men usually will not wear them; and because in spray-painting, as an example, the inlet holes soon become clogged. Acid drinks, citric acid, phosphoric acid, lactic acid and sulphuric acid lemonade are of value. The investigations of Aub and Minot[1] indicate that such drinks, or the acidosis of starvation, promote the liberation of lead from the bones where it is stored with calcium and phosphate; a low calcium-containing diet, or conditions producing a negative calcium balance in the body, is followed in lead cases by increased excretion of lead. Ammonia chloride changing to urea and liberating hydrochloric acid in the body, is, according to Haldane, another way of ingesting acid. Milk probably deserves its reputation as a preventive of lead poisoning as it produces a positive calcium balance and favors storage of the absorbed lead in the tissues but it does not prevent absorption.[2] Protein food by taking up the free HCl of the gastric juice probably prevents to some degree the solution of lead ingested. Fats, such as olive oil, also seem to have some preventive action. Exercise in the open air, by increasing eliminative functions and general resistance, has a most important influence; companies owning their workmen's houses have built them at a distance in order to necessitate a daily walk, with beneficial results.

When poisoning has developed, exclusion of the source is the first imperative necessity. In industrial cases this means, of course, a change of occupation, or, if necessary, cessation of work; in accidental poisoning it often means painstaking and extended search for the source.

Treatment.—The active treatment consists in elimination of the lead and of general products of metabolism, and in combating symptoms. The initial action should be to expel any lead in the gastro-intestinal tract, preferably by saline purges; purgatives that act largely through increasing peristalsis should not be used. Purgation is frequently difficult to accomplish, for the constipation is often obstinate if there is colic and sometimes when there is not. In such cases it is often necessary to use large and frequent doses of salines (which may have to be combined with simple enemas, or enemas containing a half ounce or an ounce, 15 to 30 gm., of magnesium sulphate), and to give with the purgatives, to control the intestinal spasm, moderate doses of atropine, pilocarpine, or other antispasmodic. The salines themselves may be antispasmodic as the colic ceases with successful purgation; they do not increase the excretion of lead. Large oil enemas are also very useful and entirely harmless. In cases with severe colic a movement may sometimes be secured only by giving moderate doses of morphine before the purgatives. Benzyl benzoate has been advocated and mineral oil is often useful. Control of the constipation is one of the most important features of the treatment of

[1] *Jour. Indust. Hyg.*, August, 1924.

[2] Aub, Minot, Fairhall and Retznikoff: *Absorption and Excretion of Lead, etc., Jour. Am. Med. Assn.*, August 23, 1924.

colic. After the bowels are once opened they should be moved at least once (better two or three times) a day until the local symptoms disappear, in order to encourage elimination and prevent return of the spasm. Water should be drunk freely, and diuretics given if the secretion of urine is low.

For persistent colic, atropine and pilocarpine, alone or with morphia may be used: pressure on the abdomen is usually comforting, and during the height of a spasm, amyl nitrite inhalation gives relief but chloroform or ether may be necessary. Warm applications with opium and belladonna by mouth or rectum will help but opium must be used with care as free purgation and elimination are desired.

The most interesting detail of treatment is in connection with lead excretion and its detachment from the body cells, particularly from the bones. Aub, Minot, Fairhall and Retznikoff outline a low calcium diet and give with it either ammonium chloride (8 to 12 gm. daily) or 20 to 25 cc. of dilute phosphoric acid which may be sweetened. Ammonium chloride, changing to urea, liberates hydrochloric acid. The negative calcium balance and the "acidosis" seem to cause increased excretion of lead in the feces, not in the urine. With a positive calcium diet (full milk diet, calcium rich diet), the lead is stored in the bones particularly, and one temporizes, as it were, with the lead excretion. Alkalies in some manner promote excretion and so does potassium iodide, but neither soda bicarbonate nor iodide has the effect of the "acid low-calcium" treatment. No untoward effects were observed in any patient though many of them were heavily leaded. The explanation of many remarkable instances of poisoning appearing months and years after removal from exposure now seems clear. Lead stored in large amounts in the bones was probably brought into the circulation by some upsetting of metabolism and symptoms resulted. Intravenous treatment by sodium thiosulphate is urged by some. Oliver speaks of good results in the relief of pain and paralysis by the oral administration of sodium monosulphite and Legge saw it in daily use as a preventive in an English lead works. In 1920 Ravaut[1] suggested its use in the treatment of the dermatitis following the administration of arsphenamine (4 to 15 gr. a day by the intravenous method was advised) and he considered that an insoluble sulphide of the metal was formed. Ockerblad seems to have been the first to use this drug in the way described for relief of symptoms due to lead. McBride and Dennie[2] claim that all metallic poisonings respond to the intravenous use of sodium thiosulphate, the drug detaching the metal from its protein combination and making it a non-soluble sulphide yet one which can be excreted even by the urine. As the drug is well borne, and as the results in arsenic and mercury cases seem very definite, its use can be urged. A 20 per cent. solution is employed and 0.3 to 1 gm. may be given intravenously daily for several days.

The electrolytic bath treatment for the elimination of lead, first suggested by Serafini and later adopted by Oliver, does not seem to have proved its claims in the opinion of Legge, Goadby, Oxley, and others

[1] *Presse Medicale*, January 28, 1920.

[2] *Arch. Dermatol. and Syphilis*, 1923, No. 7; *Jour. Am. Med. Assn.*, December 27, 1924.

who have tried it. Their experiments were equally convincing in their failure to extract lead from heavily leaded animals. It must be noted, as stated by Oxley, that the slow rate of tissue penetration by traveling ions of metal, makes the procedure almost a physical impossibility; Pack, Underhill and co-workers[1] are more emphatic and say that not only do they fail to demonstrate metals in the bath but that the theory is not based on sound physics.

Paralysis should be treated by the general principles used in managing peripheral neuritis. Active treatment should be begun only when the acute progress of the palsy has ceased. The most important measures are electricity, carefully graduated massage with passive exercises, and, so far as possible, very slowly increased active exercise. The treatment must be long-continued, and if complete recovery does not occur it should not be stopped until all improvement has ceased for months. Since there is usually decided impairment of the general health in these cases, general treatment is almost as important as local. Moderate general exercise, provided the paralysis permits of it, should be used after preliminary rest in bed; fresh air, sunshine and a generous diet must be insisted upon at all times when they can be had. Bitter tonics are useful. Strychnia is not in as good repute as a cure for paralysis as it once was, but is an excellent general tonic and will do no harm if used only after evidences of increase in the paralysis have ceased. The usual anemia needs fresh air and food, especially; but small doses of arsenic ($\frac{1}{100}$ gr. continued for only short periods, as arsenic also causes nerve-degeneration) will often improve both the anemia and general nutrition. Iron is not very effectual in such anemias, and if given should be used sparingly, lest it disturb digestion and increase constipation. The general measures mentioned are likely to be necessary in any case, whether paralysis is present or not, in order to secure recovery of good, general health.

Cerebral symptoms need to be managed with much care. The general treatment as described above is applicable; sodium thiosulphate should be used at once. There is so much danger of exhaustion that severe eliminative measures should not be used. The bowels must be kept moderately active, and diuresis should be stimulated by free water-drinking. Convulsions or delirium should be treated with large dose of bromides, combined with hyoscine or chloral. Hot packs are sometimes useful. Morphine should not be used except as a last resort, and then with care, because of its interfering with elimination. Moderate venesection is a more suitable measure in actively severe cases than is generally taught; there is sufficient evidence of cerebral congestion to justify it in such cases. Good results have been obtained from lumbar puncture, and it is reasonable to use it if the cerebral symptoms are persistent and urgent; in several of Gibson's cases an excessive amount of fluid under a high degree of tension was found.

In both prophylaxis and treatment it is of the greatest importance to exclude alcohol absolutely.

[1] *Am. Jour. Med. Sci.*, 1924, **167**, 625.

ARSENIC POISONING

Arsenic poisoning in the arts and trades is becoming less and less common as the rules and regulations applying to dangerous trades are being understood and enforced; occasional accidental poisonings occur as a result of admixture of arsenic with food or drink; poisoning, the result of the therapeutic administration of arsenic has become a common accident in the treatment of syphilis and the occasional overdosage with arsenic in the treatment of anemias and chorea is still seen. The most intense form of arsenic poisoning, by arseniuretted hydrogen gas, has attracted much attention both by the severity of its symptoms and by the various odd ways in which it has been caused. An extraordinary range of conditions has been brought into relationship with arsenic. Such affections as tar-worker's cancer, chimney-sweep's cancer, mule-spinner's cancer and cancer of the bladder in aniline-workers, are attributed to arsenic in the tar, soot, mineral oil and aniline. Only the more chronic intoxications are considered here. Like lead, arsenic has a predilection for the lower motor neurons but, it is more neurotoxic, as it attacks the sensory system of nerves as well. Like mercury, arsenic produces severe degeneration in the kidneys, while its action on the liver is at times comparable to that of phosphorus or the toxins which produce acute yellow atrophy. Poisoning by arseniuretted hydrogen (arsine) gives a picture quite distinct from that of arsenic and its salts; a quickly progressing destruction of the blood takes place, followed by degeneration of the liver and kidneys and death from toxemia in nearly 40 per cent. of cases. For purposes of more accurate description arsenic poisoning may be considered under the two headings: (1) Industrial Poisoning and (2) Therapeutic and Accidental Poisoning.

I. **Industrial Poisoning.**—Pure metallic arsenic is innocuous; the dusty white arsenic "arsenious acid" (made by roasting the ore and volatilizing the arsenic), the salts of arsenious acid, and its anhydride are the poisonous elements. Paris green, emerald green, Schweinfurt green, an aceto-arsenite of copper, is dangerous when dry and powdered. Scheele's green (arsenite of copper), formerly used in the manufacture of artificial flowers, wall-papers, and in the coloring of toys, woolens, and dress goods, has been replaced by aniline color and poisoning from this source is rarely seen. Legge[1] states that wall papers have been found to contain as much as 60 gr. per square foot. The United States Department of Agriculture notes that since the State of Massachusetts passed a law in 1900 limiting the amount of arsenic in wall-papers and woven goods that a proportion of 0.1 gr. per square yard is rarely exceeded. The arsenic dust produced in the manufacture of sheep-dip (white arsenic, caustic soda and flowers of sulphur) is dangerous as is that of a new insecticide, lead arsenate. Oxide of arsenic, used to preserve furs, skins, and hides, orpiment (AS_2S_2) a depilatory in the tan-yards, and arsenious acid powder in which bird skins are packed, poison a certain number of workers. Careful handling of the dust problem has made poisoning by arsenic and its salts

[1] In Kober and Hanson Diseases of Occupation, etc.

almost non-existent in Great Britain; no cases were reported in 1922, 1 in 1921 and 3 in 1920. A few cases were formerly reported in connection with the smelting of lead and zinc and with the process of de-arsenicating sulphuric acid. In America fume poisoning from smelting is still seen and in the manufacture of Paris green it is evident that means of prevention are not fully made use of, for the Illinois factory inspection reports give details of 20 cases of poisoning in a year in a force varying from 16 to 170 workers. The dangers of the use of arsenic in the fur trade are referred to by Gilman Thompson.[1] It is stated that as much as 170 gr. of arsenic were contained in sample square yards of fur; anti-fouling paints used on ship's bottoms occasionally poison a "paint-chipper" and shot-makers are exposed to arsenic dust. Large quantities of arsenic are used in compounding glass, but few cases are reported from the glass-works.

Deserving of special mention is the severe intoxication following the inhalation of arseniuretted hydrogen gas. Metals such as iron, zinc, copper and tin, in contact with mineral acids which contain arsenic as an impurity produce the condition necessary for ASH_3 production (nascent hydrogen plus arsenic); the arsenic impurity in sulphuric or hydrochloric acid in iron tanks has caused the death of men sent to clean the tanks. Dipping metals into acids for "pickling," making zinc chloride from waste zinc and hydrochloric acid are processes which evolve the gas if the arsenic is present in the heavy metal or in the acid. The cyanide process of gold extraction may poison workers if the zinc-dust filters are arsenic-containing, while in recent years the aniline industries, and the makers of benzidene have found that arseniuretted hydrogen poisoning from the zinc and hydrochloric acid used in the reducing process has become an established fact and explains many of the curious symptoms ascribed to absorption of aniline.[2]

II. **Therapeutic and Accidental Poisoning.**—Arsenic in various forms is much employed in therapy, has long been used for malicious poisoning, and occasionally has poisoned large groups of people by getting into food and drink. The arsenical preparations are used in chorea, primary anemias, Hodgkin's disease and skin troubles, and mild poisoning by overdosing with arsenious acid, Fowler's and Donovan's solution is not uncommon. Very severe intoxications are seen from the organic compounds, atoxyl, soamin, sodium cacodylate and the newer arseno-benzol preparations. Arsenic pastes and powders are absorbed by the broken and even unbroken skin. Historically interesting is the fact that the "Aqua Tofana" contained arsenic, while the criminal records abound in instances of poisoning by the tasteless and odorless arsenious acid, a slow death being the object in view. The ingestion of arsenic in food and drink is uncommon, sprayed fruit and vegetables occasionally poison the consumer, gross carelessness in the use of containers which have previously been used for carrying arsenic solutions accounts for most cases. The celebrated Manchester-Salford "beer poisoning" of 1901, in which 6000 persons were affected with 70 fatal results, was caused by arsenic in

[1] *The Occupational Diseases*, New York, 1914, p. 162.

[2] Hamilton: *Industrial Poisoning in Making Coal-tar Dyes, Bull. of U. S. Bureau of Labor Statistics*, No. 280.

sulphuric acid, which was used in the preparation of the brewing sugars.[1] The poisoning from wall-paper in newly-papered rooms is no longer met with, di-ethyl-arsine, produced by the growth in the paste and paper of a mold. The Penicillium brevicaule was the cause.

Pathology.—Whether arsenic enters the body through the veins, mouth, skin or lungs its effects may be the same throughout. Applied to the skin as a paste or reaching it as dust or spray, its effects may remain localized as an ulceration. Long application in such industries as pitch, tar or paraffine manufacture will eventually cause epitheliomatous degeneration; mule-spinner's scrotal cancer and chimney-sweep's cancer are now considered as results of arsenic irritation. Pigmentation, keratosis, dermatitis, herpes, erythema, and other skin lesions are the more common skin manifestations. Marked œdema may be in evidence, particularly of the legs and eyelids, and inflammation of the conjunctival sacs, of the nasal and pharyngeal mucous membranes is seen. Ulceration of the nasal septum is a common finding in those exposed to arsenic dust. Jaundice is described as occurring subsequent to the absorption of arsenic in any form or by any route; it is certainly most often seen after inhalation of arseniuretted hydrogen or the giving of arseno-benzol compounds. A degeneration of the mucosa of stomach and bowels is seen even when the arsenic has not been taken by mouth; in the liver a condition ranging from fatty infiltration to acute atrophy results, and the destruction may be extreme, jaundice occurring with such lesions. Nephrosis or a hemorrhagic glomerulonephritis occurs in the kidneys. Fatty degeneration of the myocardium and of the skeletal muscles is described and occurs early. The nervous system shows no gross lesions; the neuritis is due to the affinity of the poison for the lipoids of the myelin shealth. The glossy skin and erythro-œdema of the extremities are probably neuritic manifestations. The pigmentation is from deposition of some organic compound (Cushny). Poisoning by arseniuretted hydrogen shows in addition the evidence of active blood destruction, hemorrhages into the skin and elsewhere, signs of bone-marrow destruction and activity, and a hemorrhagic inflammation of liver and kidney.

Arsenic is taken up largely by the liver where it is quickly reduced; much is retained in the bones and in the hair and nails; excretion begins quickly by way of kidneys, bowels and skin, and the local effects are thus produced. The bladder cancers of aniline workers may be due to arsenic in the urine, skin cancers are reported as occurring after continued arsenic medication (Pye-Smith) nursing mothers taking arsenic have poisoned nursing infants (Edsall). Very little arsenic reaches the fetus in utero, in treatment of a pregnant syphilitic woman there is but slight chance of poisoning the child. The arsenic is largely retained in the maternal liver and in the placenta (Underhill and Amatruda)[2].

Susceptibility and Pathogenesis.—Variations in susceptibility are marked; arsenic eaters have been known to take 5 and 6 gr. of arsenic at a dose over a long period of time without showing poisonous effects; patients on the other hand are often prostrated by the initial intravenous

[1] Legge: In Kober and Hanson *Diseases of Occupation*, etc.
[2] *Jour. Am. Med. Assn.*, December 15, 1920.

dose of the organic compounds or by less than an ounce of Fowler's solution taken over a period of weeks (Edsall). Details of the influence of season, race, sex, age, habits in the incidence of arsenic poisoning are lacking and only one case due to occupational poisoning is recorded in the Toronto General Hospital records.

Symptoms.—In employees in the dusty trades, tree-sprayers, painters, and handlers of arsenic-containing materials, a local irritation of the skin, acne, chronic ulceration, furunculosis, dermatitis, urticaria or erythema may be the only symptom. Ulcerations of the scrotum and feet are seen in the tree-sprayers. Ulceration of the nasal septum is a common lesion among the Paris-green makers and packers; continued exposure may end in epitheliomatous degeneration of the skin. Constitutional symptoms of arsenical poisoning are rarely seen today in the workers with arsenic, its acids or its salts; generalized pigmentation, brittleness and thickening of the nails may occur, though it would seem that this condition implies more often inhalation or ingestion. The inhalation of fumes and dust, the steady administration of arsenic as a medicine or poison by mouth, may produce skin manifestions. After a long period the epitheliomatous degeneration may take place.[1] Generalized skin affections, such as dermatitis exfoliata and keratosis more often follow medical treatment. Œdema of the eyes and skin frequently follows the administration of Fowler's solution, one of the writer's cases showing gross œdema to above the knees. A coryza-like condition of the eyes and nose is an early symptom. If exposure persists or the drug is continued, there may ensue headaches, arthritis, vasomotor disturbances, cardiac distress, nervousness, mental dulness, weakness, indisposition for food, gastro-intestinal symptoms, colic not unlike that due to lead and perhaps jaundice with a large painful liver. This last is seen more often in poisoning by arseniuretted hydrogen and the intravenous preparations. Emaciation and anemia may be marked. The typical picture of arsenical neuritis may be produced. Albuminuria, hematuria, suppression of urine and signs of kidney damage are most usual after the inhalation of arseniuretted hydrogen or after the intravenous administration of the organic compounds.

The *neuritis* has been most often recorded after the ingestion of arsenic, Legge reports 6 cases due to inhalation of arsenic fumes from coke used in the ironing-room of a laundry. Intravenous medication is responsible in some cases; paresthesias, pain, at times very severe, and erythromelalgic symptoms precede the paralysis. The feet are more often affected than the hands and both foot- and wrist-drop are seen; occasionally the paralysis is permanent. Cases in which an extreme degree of ataxia is present may confuse the diagnosis and tabes may be suspected. Paralysis of single nerves, such as the recurrent laryngeal or motor oculi, may occur, and blindness is recorded. Such incidents seem more common since the introduction of the intravenous methods of treatment and the question of a local Herxheimer reaction has been raised. All sensation is eventually lost. The flexors and extensors suffer to almost the same

[1] O'Donavan: *Brit. Jour. Dermatol. and Syphilis*, November, 1924

degree although the affection of the former may be most in evidence; the supinators are not spared as in lead. Rarely a polyneuritis occurs. Atrophy of the muscles is pronounced and contractions are frequent. The reaction of degeneration is found and the reflexes naturally disappear early. The sphincters are not involved. In typical cases paralysis does not extend above the knees and elbows.

It is both a peripheral neuritis and a neuronitis.[1] Animal experimentation produces much the same picture as does poisoning by lead and shows that lesions occur in the meninges and in the white and gray matter of the brain and cord. Inhalation of dust and fumes of arsenic and the ingestion of the drug are usually necessary to produce neuritis. Paralysis is rare after intravenous administration although some signs of sensory nerve irritation are often noted. In 30 cases of arsenical poisoning following intravenous therapy in syphilis at the Toronto General Hospital, 1919 to 1924, there was no outspoken neuritis. Strathy, Smith and Hannah noted peripheral neuritis in 2 of 58 cases of delayed arsenic poison from intravenous administration. Schamberg and Greenbaum[2] in reporting a case of this sort state that the condition is less often recorded after arsphenamine. Duhot noted 5 cases, all subsequent to the use of neo-arsphenamine. Other observers have observed polyneuritis after the injection of the arsenic compounds.

Unusual symptoms are seen in the patients poisoned by the intravenous administration of arsenic. Sudden death, or death in a few hours with symptoms of collapse and toxemia may occur; Weis[3] reported 21 such cases in New York in six years and cardiovascular-renal disease was present in 13 of these, status lymphaticus in 3, and in the others no definite cause of death was determined. A systemic reaction, chill, fever, malaise, diarrhœa, nausea and vomiting with collapse symptoms are not infrequent. Œdema, itching of the skin and a long-persisting dermatitis exfoliata are seen. A severe reaction in the liver, giving rise at times to a picture of acute yellow atrophy, is a well-known happening. Weis reports 8 fatalities in the arsenic-jaundice cases in New York, while Strathy, Smith and Hannah in 1917 and 1918 had the same number of deaths among 58 cases of "jaundice with symptoms of liver atrophy." Meirowsky's statistics, based on 225,780 injections of arsphenamine and neo-arsphenamine, show that jaundice may occur once in 2000 and 6000 injections respectively. Milian of Paris considers the reaction due to death of the spirochætes in the liver and a subsequent "Herxheimer" effect. Herxheimer and Gerlach consider that the "liver atrophy" is syphilitic and its following an arsenic administration merely coincidental. That a coincidence of infectious jaundice, syphilitic jaundice and arsenical jaundice may occur in certain seasons is made apparent by the report of Stokes, Ruderman and Lemon.[4] Schamberg and Greenbaum urge caution in accepting these views and state that in their opinion every case of jaundice occurring after the use of arsenicals should be studied

[1] Kolmer and Lucke: *Arch. Dermatol. and Syphilis*, 1921, **3**, 483; Hassin: *Arch. Neur. and Psych.*, September, 1921.

[2] *Jour. Am. Med. Assn.*, January 17, 1925.

[3] Ibid., February 21, 1925.

[4] *Arch. Int. Med.*, November 15, 1920.

with the greatest care and that the continuance of the arsenic in the face of a developing jaundice can only be permissible if the arsenic can be proved innocent of the distinctly serious results seen. Severe nephritis occurred in 2 of Strathy's cases; hematuria and suppression are not unusual and albuminuria accompanies 50 per cent. of the poisonings. Fatal aplastic anemia subsequent to the injection of neo-arsphenamine is noted by Finberg,[1] Goerke, and by Moore and Keidel. Purpura, bleeding from the gums and stomatitis occur occasionally. The resemblance of the symptoms to those produced by arseniuretted hydrogen is striking; it has not been proved that the contemporaneous administration of mercury to the syphilitic receiving arsenic increases the tendency to jaundice or hemorrhage.

A convenient classification of the after-effects of the arsenic treatment of syphilis may be given as: (1) Nitritoid crises, vasomotor symptoms and rashes of erythematous or urticarial types. (2) Herxheimer reactions, though it is to be remembered that arsenic in any form or in any disease may damage the liver. (3) Acute arsenic poisoning. (4) Chronic arsenic poisoning (Stuart and Maynard).[2] Poisoning by arseniuretted hydrogen has likewise a symptomatology differing from that of arsenic proper: a minute amount only of the gas is necessary to produce a fatal result; symptoms appear in a few hours after inhalation and take the form of nausea and continued vomiting, jaundice ensues in forty-eight hours and is intense, hematuria and hemoglobinuria follow, and there may be suppression of urine. Destruction of the liver, destruction of the blood (hemolysis) and acute hemorrhagic nephritis are the chief pathological findings. In patients who recover it is unusual to find the chronic skin affections or the neuritis seen after poisoning by the other forms of arsenic; bronzing of the skin may be intense.

Diagnosis.—Weakness, anemia, nervousness, persistent gastro-intestinal symptoms, frontal headache, persistent coryza, laryngitis and conjunctivitis suggest excessive arsenic ingestion; an increasing pigmentation, keratosis and scaly skin lesions are more suspicious: jaundice, signs of liver atrophy, hemolysis, hemorrhagic nephritis, and dermatitis exfoliata demand an investigation into the possibility of a patient's exposure to arsenic or its compounds. The pigmentation, skin lesions and coryza are the only conditions peculiar to arsenic poisoning: the detection of arsenic in the urine, feces, scales, hair and nails should be attempted and is diagnostic. An unexplained polyneuritis or peripheral neuritis, particularly if associated with pain, redness and swelling, speaks for arsenical neuritis rather than one due to lead. The tests for lead and arsenic should be made and the blue line and basophilia of lead absorption should be looked for. The detection of arsenic in the secretions might be necessary to distinguish from an alcoholic neuritis (arsenic in beer has been considered as a cause of alcoholic neuritis). An arsenical origin must be considered as a possible cause for some paralysis of cranial and other nerves in arsenic-treated syphilitic patients. The legs show the greater affection in arsenic poisoning and the supinators are spared if the

[1] *Jour. Am. Med. Assn.*, March 25, 1922.
[2] *Arch. Int. Med.*, November 15, 1920.

arms are affected; cases of ataxia with the neuritis and paralysis of the legs as described by Dana, if of syphilitic origin, would be distinguished by their probably showing a positive Wassermann reaction. Sphincter involvement does not occur with arsenic poisoning. The finding of arsenic in the feces or urine would be of value. The perforation of the nasal septum, so common among the workers in arsenic dust, must be distinguished from that due to syphilis; the arsenic ulcer never attacks the bone and the "saddle nose" and destruction of the tip of the nose do not follow. Persistent ulcers of the scrotum or body, and epitheliomatous degenerations on the arms, may suggest exposure to arsenic in the form of sprays, dust, pastes or in tar-pitch-paraffin aniline and mineral oil. The history will probably be conclusive but a section of the ulcer should be made.

Prognosis.—One cannot foretell whether neuritis, dermatitis or severe liver and kidney destruction may finally ensue from the arsenic already absorbed; fatalities are to be expected in the two latter conditions. Neuritis is usually recovered from although there is an occasional case of permanent paralysis with contractures. Œdema disappears quickly when the arsenic is withheld and the pigmentation and keratosis are not permanent. The tremor and nervousness of chronic cases cease when the exposure to the poison stops. The ulceration of the skin is always chronic and epitheliomatous degeneration cannot be forestalled. Recovery from the most severe liver atrophy may be seen. Poisoning from arseniuretted hydrogen will be fatal in nearly 50 per cent. of cases.

Treatment.—Removal of the patient from the exposure to arsenic dust or fumes, and withholding of the arsenic preparation are essential. It is impossible to protect from arsenic dust by any form of inhaler, since ulceration occurs around the edge of the mask, Dunlap's description[1] of the nasal septum perforations from arsenic in the copper-smelting industry shows well the difficulties of treatment; large ulcers and epitheliomata are usually excised, metastasis being unusual. The sodium thiosulphate treatment seems to be sometimes efficient in treating the arsenical dermatoses[2] (see under lead); it is also urged in the treatment of liver degeneration, jaundice, and all systemic symptoms. A careful analysis of 2 cases of this nature treated in the Toronto General Hospital by sodium thiosulphate allows no conclusions to be drawn; equally severe cases under the writer's observation have recovered without the use of the drug. Its use in cases of chronic ulcerative lesions is not reported. If like lead, arsenic is stored in the bones and liver the "acid calcium balance" theory treatment may be considered. For the symptoms due to hepatic insufficiency, nausea, vomiting, diarrhœa and thirst, high carbohydrate feeding is suggested, based on the theory of a glycogen exhaustion, as in the nausea and vomiting of pregnancy (Harding[3]), glucose can be given by mouth, bowel or into the veins. The neuritis may require the use of an analgesic in the beginning; massage and electricity are useful in restoring the muscle power.

[1] *Jour. Am. Med. Assn.*, February 26, 1921.
[2] Bugg and Fulkoff: *Bull. Johns Hopkins Hosp.*, March, 1924, p. 76.
[3] *Lancet*, 1921, ii, 327.

Transfusion should be tried in the cases of hemolysis due to arseniuretted hydrogen, the use of iodide in arsenic poisoning follows the same lines as in the section on lead. It may have value but results claimed for the sodium thiosulphate in such conditions as "arsenical encephalitis"[1] have at present discounted other methods of treatment.

MERCURY POISONING

Mercury appears as a poison in the industries, may be the cause of serious symptoms when given as a drug, is a substance frequently swallowed by accident or used carelessly, and is used as the agent in suicide or murder. In the industries only the cases of chronic mercurialism are known to occur; in the therapeutic and accidental poisonings, acute, subacute and chronic effects are noted.

I. **Industrial Poisoning.**—Mercury, existing as "free silver" or quicksilver in some mines, poisons quickly since it is volatile at low temperatures (85.5° F.), and men sicken in two weeks and less; the poisoning from "free silver" has made some Californian mines unworkable. For centuries it has been realized that in the mines at Almaden and at Idria, the laborers, convicts or slaves, could work only a few hours a day and for but a month at a time. Mercury ore, Cinnabar (HgS), is apparently innocuous until the process of smelting begins; some poisoning may be due to the Cinnabar dust getting into cigarette tobacco while the worker rolls his cigarettes.[2] The recovery of mercury from the soot, dust, and condensers exposes the employees to the vaporizing metal or to finely divided particles of mercury which may be inhaled or swallowed; mercury in the miner's clothes may poison those who continually handle them. Kober states that 10 per cent. of the New Almaden miners in California suffer from mercurialism. Improved conditions in the Idria mines and smelters cut down the cases of mercurialism from 122 in 1896 to 5 in 1908; mercury poisoning in England, where there are no mines, occurs in the barometer and thermometer works, in fulminate explosive manufacturing, in the making of feltings for hats and in fur cutting—mercuric nitrate being extensively used in the felting process. There were only 5 cases reported for 1920, and none in 1921-22. Other occupations which may give rise to mercury poisoning are mirror making, electric light bulb making (using of mercury pumps), taxidermy, the making of anti-fouling paints, coating of electrodes with amalgam, soldering with mercury in dry-battery work, fire gilding, water gilding, the amalgam process in the McArthur-Forrest cyanide method of treating gold and silver ore. Mercury mirror backing is replaced largely by a silver-nitrate process save in parts of Europe, and water gilding has given way to electroplating. Mining, smelting, the carotting of fur for felt making, and the felt making itself contribute the bulk of cases on this continent: Harris[3] found that of 266 fur-felt workers, 212 were exposed to the mercuric

[1] McBride: *Jour. Am. Med. Assn.*, March 7, 1925.

[2] Hamilton: *Mercurialism in the Quicksilver Production in California, Jour. Indust. Hyg.*, 1924, 5.

[3] *Dept. of Health, City of New York, Monograph*, Series No. 12.

nitrate used; of these, 40 had gingivitis and tremors while 91 had tremors of greater or lesser degree. Bates[1] in an investigation for the National Civic Federation in 1914 reported many cases of tremor and the occasional incidence of complete paralysis or multiple neuritis. Occasional poisoning is seen in the process of manufacturing calomel, bichloride and other salts.

II. **Therapeutic and Accidental Poisonings.**—In hypersensitive subjects a single dose of proper therapeutic size, a mercury rub or a vaginal douche of bichloride solution may give rise to an acute poisoning, or may be followed later by stomatitis, tremors, or rarely, neuritis; repeated dosage is usually necessary to produce this effect and only rarely do we see the specific nervous signs of chronic mercurialism as the suggestive signs in the mouth call a halt to the mercury administration. It is suggested that at times the tremor and excitability of early syphilis of the nervous system may be caused or aggravated by mercury. Lucke and Kolmer[2] call attention to the similarity between the lesions of general paresis and those produced in the brain experimentally by chronic mercurial intoxication. The majority of the cases of chronic mercurialism seen apart from industrial poisoning come from exposure to mercury vapor about induction furnaces in laboratories. In former times vulcanized teeth plates contained more cinnabar and vermilion to give the "gum" color and intoxications were recorded. Edsall speaks of two dentists poisoned by rubbing up amalgam in their palms, a performance still carried on. A case referred to the writer showed only the local signs of thickening and cracking, and arsenic in the zinc filings might be responsible in this case for the skin changes. Even the mercury in a tooth-filling may poison, and poisoning from cosmetics containing mercury has been frequently reported. Chemists, druggists and others handling mercury and forgetful of its volatile qualities suffer at times from the chronic form of intoxication.

Method of entrance of mercury into the body. Most of the easily evolved vapor goes to the lungs direct and thence into the general circulation and probably for this reason, miners, smelters and workers with metallic mercury show early the severe cerebral symptoms. The more dusty preparations or finely divided mercury in the dust or on the hands caught in the nasal and oral secretions, reach the stomach and intestines to be absorbed into the liver and apparently be excreted again into the large intestine, which, in poisoning, always holds more mercury than the rest of the tract. Medicinal dosages follows the same course. Mercurial preparations are quickly absorbed by the vaginal or rectal walls and by wound surfaces. Mercury in oils and fats goes readily through the skin. Mercury in amounts of 0.02 mg. per cubic foot of air will give signs of poisoning in two to three months and absorption of from 0.77 to 1.825 mg. will take place in an exposure of three to five hours in such an atmosphere.[3] Mercury is probably largely stored in the bones and liver; excretion by

[1] *Monograph of Women's Welfare Department of National Civic Federation.*
[2] *Arch. Neurol. and Psych.*, September, 1923.
[3] Turner: *Pub. Health Reports U. S. Pub. Health Service*, February 22, 1924, Treasury Department.

the saliva, intestine and kidney takes place after all routes of absorption and is attended with severe damage at the points of exit.

Pathology.—The stomatitis is due to the ulceration of the soft parts produced by the excreted mercury; the gums and mucous membrane about carious teeth suffer most. The bones of the jaw are affected by contiguity in deep ulcerations but not primarily and specifically as in phosphorus poisoning. A blue line like the lead line may be seen. Letulle[1] describes a process resembling that seen in insular sclerosis in the nervous lesions produced in animals. Kolmer and Lucke[2] find thickening of the pia-arachnoid and cellular overgrowth, proliferation of the capillary endothelium and new-vessel formation, a condition in general much like that produced by lead and arsenic. Mercury has been found in the brain in fatal cases of mercury poisoning. The paralyses due to mercury are not as a rule associated with wasting and atrophy, Letulle claimed that the axis cylinder processes were preserved; the description of some cases however suggests a neuritis. The few skin lesions described have been of erythematous and eczematous nature. A chronic kidney and liver degeneration is described and deposition of calcium in the kidney calices has been frequently noted.

Symptoms.—The symptoms in the industrial poisoning are distinctive. Mercurial pallor has long been associated with mercury miners. The repeated absorption of vaporized mercury produces certain acute nervous symptoms; after a varying time of exposure, foul breath, joint and muscle pains, anemia, weakness and loss of appetite are noted, followed by gastro-intestinal disturbances and headache: diffuse stomatitis of a mild degree begins early and may progress to ulceration and loss of teeth but ptyalism is not a marked feature of the stomatitis. A peculiar copper red discoloration of the pharynx and fauces with a copper-colored line on both upper and lower gums as well as numerous small erosions are described by Kussmaul, Teleky and by Turner. Wright[3] noted the blue-black gum line in 3 of 108 hat-fur workers examined for mercurialism. Giglioto saw 30 severe cases of stomatitis in a force of 175 miners and mentions punctate hemorrhages in the skin, nosebleed, enlargement of the liver and anosmia. Continued exposure produces the peculiar mercurial erethism and tremors; the erethism has with it a state of bashfulness and self-consciousness which is considered as belonging peculiarly to mercury poisoning; in the presence of a stranger all volition may seem to be lost. Preceding the tremors there may have been a history of nocturnal cramps and spasmodic muscle contraction; the tremors range in amplitude from the fine regular movements of a thyrotoxic condition to the gross activities of an intention tremor or the clonic spasms of epilepsy. The muscular weakness is extreme and speech may be interfered with by the tremor of lips and tongue, and the gait be markedly affected: psychic symptoms may supervene. In any large group of cases there are instances of paralyses, possibly myelitic in origin, and of multiple neuritis; permanent crippling is spoken of in the New York Civic Federation reports. Rigidity

[1] *Cont. Rend. Acid, Scien.*, 1887, **104**, 74.
[2] *Arch. Neurol. and Psych.*, September, 1924.
[3] *Jour. Indust. Hyg.*, November, 1922, **4**.

of muscles and increase of reflexes are mentioned as the usual accompaniment of mercurial paralyses, and cases in which foot- and wrist-drop have occurred indicate that a neuritis has existed. A mild degree of anemia is usually found in the chronically poisoned patients: Turner's cases showed a lowered hemoglobin, a normal white blood count, and a lymphocytosis but basophilia is not described. Renal and cardiovascular disease is said to be a common finding in subjects of chronic mercurialism.

In therapeutic and accidental poisoning of subacute and chronic form there is the history of the administration of a toxic dose of mercury or of the continued use of the drug in some form. Poisonings from mercurochrome, the new mercurial, are in evidence.[1] The severe ulcerative stomatitis and ptyalism may have subsided, the colitis and nephrosis may have been recovered from, but weakness, anemia, possibly an erythema, tremors and neuritic signs follow and and very rarely, progressive kidney change. In the more purely accidental exposures, the exposure to mercury vapor, the absorption of mercury from teeth plates, from amalgam workings, and from the handling of mercury salts, the less severe chronic sore mouth as described in industrial poisoning, the tremors and erethism are again the prevailing symptoms.

Course and Prognosis.—Persistent exposure in the industries leads to permanent disability. In young workers the tremors and erethism will probably disappear if they are removed from the poisonous contact; in older people the tremors may persist and chronic invalidism seems a not uncommon result of continued poisoning with permanent paralyses or mental change. The kidney changes may be progressive but stomatitis and chronic skin lesions quickly clear when the source of poisoning is removed.

Diagnosis.—Pallor, chronic sore mouth and unexplained gastrointestinal symptoms are suggestive signs in mercury workers: tremors and erethism complete the picture; the blue-black line on the gums and blackened teeth are valuable aids. In those exposed, a chronic eczema or dermatitis necessitates the consideration of metallic poisoning, particularly arsenic or mercury. The detection of mercury in urine, saliva or feces should be attempted in all doubtful cases; all amalgam dentures must be considered suspect. The tremors due to alcoholism can only be differentiated by the history of alcoholism; the tremor of "age and arteries" must be thought of: other signs of multiple sclerosis will probably be in evidence by the time the intention tremor of the disease has developed. The excitability and tremor of early neurosyphilis, of general paresis, of encephalitis and cerebral arterial change may closely resemble those of chronic mercurialism. The history, the age and occupation, pupil changes, the reaction of the blood and spinal fluid with other signs of cerebrospinal syphilis, encephalitis or arterial disease must be looked for; the erethism is peculiar to mercury poisoning. Rarely has the neuritis of mercury poisoning to be distinguished from that of alcohol, lead or arsenic; like lead neuritis it lacks the sensory and vasomotor signs of that due to alcohol and arsenic. Foot- and wrist-drop are described but not supina-

[1] Bunten: *Jour. Am. Med. Assn.*, May 3, 1924.

tor involvement. Old cases with persistent gross movements or with paralytic signs may have to be distinguished from degenerations in the basal ganglia or from chronic poliomyelitic disease.

Treatment.—Further contact with mercury must be avoided or protection from vapor and dust must be assured. Since excretion of mercury may continue for weeks after poisoning (190 days in a case of Oberlander's) it seems advisable to use the sodium thiosulphate as in lead poisoning in order to prevent further damage. The same plan of treatment as laid down in lead poisoning may be followed, using iodide, ammonia, or acids to promote excretion and regulating the calcium intake as described. No one form of treatment influences the stomatitis; bland or mildly astringent mouth-washes are preferable. The sodium thiosulphate should be pushed to prevent further excretion of mercury into the mouth. Tremors and movements may be treated with hyoscine and belladonna. Little can be done for the erethism save the removal from exposure, which usually suffices; the electrolytic treatment completely fails to remove mercury from the body.

PHOSPHORUS POISONING

Acute and chronic poisonings have been described, the former being accidental, usually suicidal and produced by a massive dose; with the regulation of the match-making trade chronic phosphorus poisoning has practically disappeared. Phosphorus taken by mouth in large amounts acts very distinctively, giving a picture like that of acute yellow atrophy. The resemblance to the action of metallic poisonings is further borne out by the fact that continued exposure to the fumes of phosphorus (yellow) produces a specific lesion, necrosis of the jaw bones "phossy jaw," a sign of chronic industrial phosphorus poisoning which came to medical knowledge about fifteen years after the lucifer match appeared.

Etiology.—Acute poisoning (suicide) was practically always from the swallowing of match heads. Wittaus and Becker detail the frustration of a murder plot by the luminosity in the dark of the phosphorus placed in the food. Chronic poisoning, necrosis of the jaw, is due entirely to inhalation of fumes; formerly seen principally in match-makers it now develops occasionally in the phosphor-bronze workers (Kaup). The poisoning in this industry and that seen after exposure to fumes from ferrosilicon (which contains phosphorus) is due to phosphuretted hydrogen, is more an acute process and does not seem to be associated with jaw-bone necrosis, save in rare instances.

Pathology.—Acute poisoning by ingestion produces a remarkable condition of fatty degeneration of all organs, fatty infiltration of the liver with destruction of the liver tissue, and a picture, save for the fat accumulation, not unlike that of acute yellow atrophy. Multiple hemorrhages and signs of hemolysis are described; jaundice is usually marked. The feature of chronic intoxication from phosphorus fumes is a necrosis of the jaw bones, usually of the lower, often of both: a sclerosing osteitis and periostitis develop which interfere with the blood supply of the bone; infection from a tooth socket may start an extensive and very chronic necrosis of the bone with extensive destruction of soft parts and burrow-

ing sinuses. Phosphorism or other signs of chronic intoxication do not seem to occur.

Symptoms.—The symptoms of acute poisoning begin at once with gastro-intestinal irritation and luminosity of the breath, vomitus and feces is recorded. A period of quiet follows but within one to five days jaundice and signs of liver enlargement appear with pain in the abdomen. Symptoms of acute yellow atrophy may supervene and save for the history and the early fat infiltration in phosphorus poisoning the conditions are identical. There is persistent vomiting and diarrhœa, hemorrhages into the skin and from the mucous membranes, bowels and kidney. Fever, muscle pains and rapid wasting are usual. If recovery takes place the liver slowly reduces in size, the jaundice disappears, and health is restored. A persistent asthenia and anemia were described by older writers. The chemistry of the blood, urine and feces of the cases of acute poisoning is essentially that seen in acute yellow atrophy. The marked cerebral symptoms of icterus gravis are usually lacking. Isolated paralyses are described, due probably to hemorrhages in the nervous tissue. Fully 50 per cent. of the cases of acute poisoning die and 0.116 of of a grain has produced fatal results. Death may occur in twelve hours but the majority of fatalities take place within a week after the ingestion of the poison.

Chronic phosphorus poisoning, necrosis of the jaw bone, cases of which were seen in America as late as 1910[1] can be produced only by the inhalation of fumes from yellow phosphorus. Years of exposure are necessary for its production and an infection at the tooth socket is the usual exciting cause; infection of the hardened bone results. The periosteum affected by phosphorus offers poor resistance and very chronic forms of osteitis and periostitis with sequestration result. Suppuration in other bones, as in compound fractures, has been associated with a condition similar to the "phossy jaw." Both jaws may suffer, the process may extend to the orbits and through them to the eyes and meninges, infection and destruction of the soft parts and multiple sinus formation with extensive burrowing resulting. Hideous deformity may result and with chronic suppuration makes the victim an object of repulsion. Death from the toxemia often results or amyloid disease ensues. General fragility of the bones has been described. Late poisoning, some years after removal from exposure, suggests that phosphorus, like the heavy metals, may be stored in the bones.

Diagnosis.—In the acute cases the suggestion of acute yellow atrophy, of arsenical poisoning or infectious jaundice may be evident. The history of phosphorus ingestion may be the only cue, as jaundice does not invariably occur early in the atrophy or infectious jaundice. The acuteness of the onset and the early gastro-intestinal symptoms with rapid enlargement of the liver are in favor of phosphorus poisoning. Leucin and tyrosin are said to be more abundant in the urine in the cases of atrophy but this is very uncertain. The greater fat content of the phosphorus liver is a more definite finding at autopsy. The detection of phosphorus in the excretions is not a means of diagnosis. The history and the chronicity of the phosphorus necrosis are distinctive.

[1] Hamilton: In Kober and Hanson's *Diseases of Occupation*.

Prophylaxis.—Phosphorus poisoning has disappeared from the records of most countries. In the United States the sesqui-sulphide of phosphorus safety match and the Esch law of 1912 did away with the yellow phosphorus match and phosphorus necrosis is no longer seen, though as late as 1910 Hamilton found no less than 150 cases.[1] The prevention of the occasional case of poisoning by phosphuretted hydrogen requires supervision of the phosphor-bronze industries and provision for the removal of fumes. Strict laws have been made with regard to the handling of ferrosilicon which gave rise to wholesale poisoning on ships or in warehouses; arsine is a contributing factor in these cases.

Treatment.—Lavage or an emetic at once is indicated in acute poisoning and a purge should follow. Oil must not be given as phosphorus is soluble therein and may be further absorbed. Peroxide of hydrogen and permanganate of potash given by mouth may form the non-poisonous oxide of phosphorus in the stomach; old oil of turpentine has been given for its oxidizing effect, whether sodium thiosulphate would be of benefit is not determined; alkalies are urged to combat a supposed acidosis. No treatment has any effect upon the fatty degenerated liver and other organs but a carbohydrate diet and added glucose might be indicated. Early resection of the jaw was at times necessary in chronic cases; the indications are entirely surgical and under any treatment there was a mortality of nearly 20 per cent. The treatment of poisoning by phosphuretted hydrogen is that for arseniuretted hydrogen.

ZINC, COPPER AND BRASS POISONING

The fumes of burning zinc and the fumes produced in brass casting are responsible for a condition spoken of as zinc chills, spelter chills, zinc ague or brass-founder's ague. We have very little evidence that other commonly used heavy metals, iron, copper and tin, produce symptoms of poisoning, although Mallory[2] is strongly of the opinion that hemochromatosis represents a very chronic form of copper intoxication developed as a result of the long continued ingestion or aspiration of minute amounts of copper. In Mill's 17 cases[3] of hemochromatosis 11 had had a long exposure to copper either in their work or in the taking of distilled liquors which may contain considerable copper absorbed from the metal of the still. Copper fumes stain the hair and teeth, cause the sweat to stain the garments green, and the metal can be demonstrated in the green-stained underwear. Copper-workers and miners however are not unhealthy and symptoms ascribed to copper, save perhaps in the nickel-smelting industry, are usually due to lead, arsenic or acid fumes. Sigel[4] showed that "brass chills" occurred in foundries where no copper or iron could be demonstrated in the sublimation product and Hayhurst's observations of the "zinc chills" among the zinc-smelters of La Salles county are equally conclusive as the ores there contain no copper or arsenic and only traces

[1] Hamilton: *Inorganic Poisons Other than Lead, Jour. Indust. Hyg.*, vol. **1.**
[2] *Am. Jour. Path.*, January, 1925.
[3] *Arch. Int. Med.*, September, 1924.
[4] Sigel: Quoted by Hayhurst: *Am. Jour. Med. Sci.*, 1913, **145,** 723.

of iron and lead. The fumes in brass casting contain on an average 28 per cent. of flaky oxide of zinc and this is the dangerous element. Lehman demonstrated that the fumes from pure zinc alone were able to produce every symptom of the "brass chills" and it is now generally agreed that zinc is the sole cause.

The description of the "ague" is that it is an acute malaria-like syndrome of chill, fever and sweat appearing a few hours after inhalation of the fumes of molten, volatilized zinc, the paroxysm being preceded by dryness and parching of the throat and an irritative cough with feelings of constriction, lassitude, anorexia and even emesis. The attack ends in a crisis-like sweat; the fever is moderate in range; there is prostration for ten to twelve hours and the victim wakes with a metallic taste in his mouth and a temporary loathing for food. A full description of these phenomena is given by Hayhurst, Riesman and Boles,[1] Lehman and others. It was first distinguished from malaria by Thackrah in 1830; the curious fact that the chills are more common after a holiday (Monday chills) has been often noted; two of the writer's cases volunteered this information. Riesman and Boles observed recurring jaundice in one of their patients and say that diarrhœa is usual among the brass-moulders. It is questioned whether a tolerance for zinc fumes is acquired; some workers are still subject to chills after twenty-five years of exposure and 75 per cent. of those exposed suffer. Brass chills in themselves do not incapacitate but brass-workers are short-lived and very subject to pulmonary diseases.

Lehman ascribes the peculiar syndrome of "spelter chills" to the action of the zinc oxide on the whole surface of the respiratory tract; a superficial necrosis takes place and protein absorption with its symptoms is a result. Armit suggests that the zinc carbonyl of the fumes is the active agent; nickle fused with copper at 1500° C. evolves nickle carbonyl and may cause chills of similar nature.

Treatment.—Proper removal of fumes is all important and the only cases of zinc chills reported in Great Britain for 1920–22 occurred from the use of oxy-acetylene flame on galvanized metal and were accidental exposures. General measures are recommended for the treatment of the chill.

MANGANESE POISONING

Although poisoning by manganese was suggested as a cause for the paraplegia and paralysis seen in two manganese-dioxide workers by Couper in 1837 and although Schlokow in 1879 described the features of manganese poisoning as spinal-cord symptoms due to zinc absorption, yet as late as 1901 von Jaksh was unwilling to ascribe to manganese the peculiar nervous affections in 3 men employed as grinders of the dioxide of this metal. In this year however Embleden sensed the connection between "the paralysis agitans-like" picture and the occupation of grinding manganese and reported 2 cases in men so employed as "chronic manganese poisoning:" In the next fifteen years many contributions

[1] *Am. Jour. Med. Sci.*, March, 1917.

taught us that in a few highly susceptible subjects manganese dust can produce marked nervous symptoms. In this continent Edsall, Wilbur and Drinker[1] have confirmed Casamajor's findings[2] and have found the suggestive "lenticular disease-like" symptoms in 30 other cases.

Etiology.—Handling the dry manganese dioxide in the manufacturing of bleaching powder or grinding manganese dioxide for commercial utilization caused the disease in the reported French and German cases. To the manganese existing as an impurity in zinc ores can be ascribed the symptoms in Schlokow's cases, and, so far in this continent, it is the handling of these dusty zinc and manganese ores that has been responsible for the syndrome of chronic manganese intoxication. Individual hypersusceptibility to manganese is probably the real underlying cause.

Pathology.—Only one autopsy is recorded; the findings though suggestive are not conclusive, showing "degeneration in the longitudinal fibres in the pons, which run with those of the pyramidal tract." Stocker calls attention to the similarity of symptoms in chronic manganese poisoning and in Wilson's lenticular degeneration. The victims of the disorder have in most cases outlived their observers and experimental poisoning has produced no consistent picture.

Symptoms.—Three months' exposure to dusty ores or salts may suffice to initiate symptoms but one to three years' occupation in handling manganese is the usual history. An insidious onset with languor and sleepiness precedes the complaint of weakness in the legs. A stolid mask-like facies develops and the man is noted to speak with a slow monotonous voice; muscular twitching follows with nocturnal cramps in the calves and stiffness of the legs. By this time there is probably a fine tremor of the hands or gross rhythmical movements of the arms, legs and trunk which suggest the lenticular degeneration. Marked emotional disturbances, such as uncontrollable laughter, or, less frequently, crying, are a feature of the disorder. Propulsion as marked as in paralysis agitans is often an early symptom and retropulsion is seen; there is a peculiar slapping gait, and to descend a hill or the stairs is to invite a forward fall. Mental deterioration of a mild degree may exist but is not as a rule progressive. The older writers speak of the vacant face, the open mouth, and persistent drooling. There were no sensory symptoms in evidence in most reports.

All the reflexes are increased and well marked ankle- and patellar-clonus is present. Stretching of any muscle may elicit rhythmical contractions. There is no wasting and no real paralysis; rigidity in passive movements has been frequently described and a nodding spasm may be present. The pill-rolling movement of paralysis agitans has been seen but there is no intention tremor and no real ataxia. In testing the station the man falls when the eyes close and he cannot as a rule walk backwards without retropulsion becoming evident and he falls. Nystagmus or ocular paralysis is not usual. Manganese may be found in the urine and feces; it is excreted freely in the bile.

Diagnosis.—von Jaksh's cases were diagnosed insular sclerosis and it is from multiple sclerosis, paralysis agitans, lenticular disease, or the

[1] *Jour. Indust. Hyg.*, August, 1919.
[2] *Jour. Am. Med. Assn.*, 1913, **60**, 646, and Kober and Hanson: *Diseases of Occupation*, etc.

more unusual type of encephalitis, that manganese poisoning must be distinguished; the history of exposure is all important and the absence of the more usual signs of insular sclerosis is noteworthy. The progress is radically different as patients removed from contact with manganese recover, or remain unchanged. The gross movements are unlike the intention tremor of insular sclerosis and paralysis agitans is a development of later life and has a more limited range of tremors and movements. The differentiation from Wilson's disease and from some of the chronic types of encephalitis must be difficult; retropulsion and propulsion are unusual in the latter disorder, and the history of etiology, onset, progress and termination are essentially different.

Prognosis.—If exposure has not been too prolonged complete recovery may ensue on removal from the dusty employment: many of the patients retain their symptoms for years but they do not die of the disorder itself.

Treatment.—This consists in removal of the poisoned worker from his employment. Nothing has been of real value in the treatment of symptoms but hyoscine and pheno-barbital might be used as in the chronic spasmodic forms of encephalitis.

BISMUTH POISONING

The intravenous use of bismuth preparations in the treatment of syphilis is occasionally followed by symptoms of a mild intoxication and by signs which indicate that bismuth is excreted by the saliva, for a low-grade stomatitis may exist and a very evident black line may appear on the gums. Poisonous symptoms from wound dressings containing bismuth were described as long ago as 1887.[1] There were many cases of poisoning with the bismuth, paraffin and iodoform paste used extensively in surgical dressings in the early years of the great war. Restlessness, nervousness, a mild nocturnal delirium were considered as due to the bismuth absorbed from the extensive wound surfaces; the black line of bismuth, much more extensive than the line of lead, was the suggestive point in diagnosis. In a case of the writer's, the line was complete on both gums and surrounded completely two large ulcerative patches on the tonsils. Poisoning subsequent to oral administration is rare, although reported; impurities in the bismuth must be suspected in such cases. withholding of the bismuth is followed by disappearance of all signs of poisoning.

CHRONIC SILVER POISONING OR ARGYRIA

Argyria is of two forms, local and general. The former occurs in those who handle silver in their occupations, when it is seen chiefly in the skin of the hands, a condition first described by Lewin.[2] It may be due to prolonged use of silver preparations, particularly in hair dyes, or in treating diseased mucous membranes of the eye, throat, and other parts; de Schweinitz[3] and others have directed attention to the danger accom-

[1] *Brit. Med. Jour.*, 1887, i, 749.
[2] *Berl. klin. Woch.*, 1886, p. 17.
[3] *Transactions of the American Ophthalmological Society*, 1903.

panying long-continued use in this way of the newer silver preparations, such as protargol.

General argyria has also occurred in a few instances from prolonged occupational contact with silver, and, in a smaller number of cases, from its protracted local application. In a great majority of instances, however, argyria has been due to the therapeutic internal use of silver nitrate. In slight degree the condition has been set up by as little as 2 gm. (30 gr.) administered in the course of two months; but when marked general discoloration occurred, the amount has generally been much larger, 15 gm. (℥ss) or more. The comparatively frequent occurrence of argyria in earlier times, and the very unfortunate results, led to such general and emphatic warnings against the possible production of it that the condition has become quite uncommon.

Pathology.—Argyria consists of a deposit of silver in the skin or mucous membranes alone in the local form, in the internal organs also in the general form. In argyria due to internal use of silver, the pigment is found in the papillæ of the skin and in the glands, but not in the epithelium; in occupational cases, in which it enters from the exterior, it may be found in the epidermis. In generalized argyria most of the organs may show pigmentation, but it is ordinarily most marked in the kidneys, liver, and choroid plexus. The pigment is situated in the vessel walls and the nearby tissues. In the early stages it is first found in the leukocytes. Silver salts, when absorbed, form an albuminate, and this is gradually deposited and reduced. Chronic interstitial changes in the liver, lungs, and kidneys have been described as a result of the prolonged presence of the pigment in the tissues.

Symptoms.—The condition consists of a more or less disfiguring pigmentation without any subjective symptoms; an isolated case of neuritis with symptoms resembling the forearm-extensor palsy of lead poisoning is mentioned by Gowers. Marked mental depression and abnormal shyness may naturally result from the very marked disfigurement. As a rule, however, pigmentation is the sole result. When this is due to local application or to occupation, the discoloration begins in the areas that come directly in contact with the silver, and in such it usually remains localized. If it results from internal use of silver, the first pigmentation is almost always seen in the form of a line on the edge of the gum that resembles the lead line but is of a more violet color. This line is of diagnostic importance and also serves as an important warning, since it appears well before the pigmentation of the skin, and indicates the necessity of stopping the use of silver at once. When skin pigmentation develops from internal use, it is at first in patches, chiefly in areas much exposed to light; the patches afterward coalesce and the whole surface skin, conjunctiva, and other visible mucous membranes—ultimately shows more or less pigmentation. Slight grades resemble moderate degrees of cyanosis; in more severe cases there is a very striking and characteristic slate-gray color that makes the appearance of the individual extremely conspicuous. If distinct pigmentation is allowed to develop while silver is still being administered, the discoloration usually grows more marked after the drug is discontinued, because

a considerable amount of unreduced silver is present in the body under such circumstances, and reduction goes on for some time. The color may continue to deepen slightly for many months; in one case, it apparently continued to grow darker for years. The color sometimes varies greatly on bright and dark days.

Diagnosis.—The discoloration may be mistaken for cyanosis, and the line on the gums may be confused with the lead line. The nature of the condition is determined by the history, or, if desirable, by excising small portions of skin and finding that in sections the pigment granules disappear after treating with potassium cyanide or concentrated nitric acid, and reappear upon adding ammonium sulphide. There is no practically likelihood of mistaking the condition for anything else when the color has once been seen and recognized.

Prognosis.—Once developed, the pigmentation is permanent. If there is merely a line on the gums, disfigurement of the skin may usually be avoided by discontinuing the use of silver at once. If the skin already shows discoloration, this generally deepens somewhat, even if the drug is stopped.

Prophylaxis and Treatment.—The prophylaxis consists in the exercise of great care in prescribing silver nitrate, not giving more than one-fourth grain doses and not continuing it for more than six weeks. If it is desired to use the drug further in the same patient, there should then be an intermission of several weeks. Patients should not be given solutions of silver to use without the supervision of a physician, and they should be warned against the danger of having prescriptions refilled for internal use or external application.

There is no treatment for argyria, all practicable methods of combating the pigmentation being entirely unsuccessful.

CHAPTER XXII

I. ACUTE CARBON MONOXIDE POISONING, ILLUMINATING GAS POISONING, COMBUSTION PRODUCTS POISONING.
II. POISONING BY NITROUS FUMES.
III. CARBON DISULPHIDE POISONING.
IV. BENZOLE POISONING.
V. POISONING BY THE BENZENE DERIVATIVES.

By NORMAN B. GWYN, M.B.

I. ACUTE CARBON MONOXIDE POISONING

The dangerous element of combustion products and of illuminating gas is the carbon monoxide, and clinically it is difficult to distinguish the cases poisoned by pure carbon monoxide, by illuminating gas, or by combustion products. In industries, such as steel making or melting aluminium, the worker may be exposed to a combustion product gas containing 28 to 32 per cent. by volume of carbon monoxide, a percentage of carbon monoxide equal to that of illuminating gas. Owing to the increasing use of gas for heating and to the numberless exposures to gasoline exhausts in the care of motors, cases of carbon monoxide poisoning have greatly increased in numbers. We are more familiar with acute poisoning but undoubtedly a low-grade chronic poisoning exists. A 20 per cent. saturation of the hemoglobin with carbon monoxide gives symptoms, a 50 per cent. saturation causes coma and 80 per cent. means death.

Etiology.—Wherever combustion is going on, as in mine blasting, blast furnaces, coking plants, crucible furnaces, charcoal burning, coke braziers, mine explosions, the burning of coal fuel, gas, or gasoline, carbon monoxide is produced and may be responsible for accidental poisoning, particularly if the ventilation is deficient. In towns and cities using carburetted water gas there are numerous cases of poisoning among the gas company employees who are often exposed to leaking gas. Accidental and suicidal poisonings from unburnt gas are frequent and gas may leak into a house from a broken main outside; Edsall states that the characteristic odor may be lacking under such circumstances. Complete combustion gives off carbon dioxide; incomplete combustion, as when a gas flame strikes a cool surface, produces carbon monoxide; this is considered to be the source of many accidents when gas is used for cooking and heating. Individual susceptibility must play a part in determining the reaction to the carbon monoxide inhaled as a frequent record in dual poisonings is that only 1 of the 2 exposed to the same amount dies or that one room-mate retains consciousness while the other is deeply gassed.

Pathology.—The body may appear rosy and natural with pink-red splotches of hyperemia; if death has occurred quickly, pallor or cyanosis may be the picture. In the Toronto General Hospital records "bright red mucous membranes" or "cherry-red lips" were seen or noted only in illuminating gas poisoning; "cherry-red very fluid blood" is usually the autopsy note. Fatty degeneration of the heart muscle, liver, kidneys and vessel walls may be seen; punctiform hemorrhages in the brain, muscles, lungs, mucous and serous surfaces are common findings, while at times gross hemorrhages into pleura, pericardium, peritoneum or brain may be met with. The changes in the brain, either in those who have died directly from exposure to the carbon monoxide or later in the course of a psychosis, may be extensive; large symmetrical degenerations may occur as the result of thrombosis or encephalitis.[1] Death after three weeks from pulmonary infarct and pulmonary artery thrombosis took place in one of the Toronto General Hospital cases. The skin may show purpura, pemphigus, blisters or herpes, and extensive areas of gangrene have been seen. The color of the body and blood is due to carboxyhemoglobin, the combination formed by the union of carbon monoxide and hemoglobin; decomposition is postponed in bodies with highly saturated carbon monoxide blood. The affinity of the hemoglobin for carbon monoxide is 300 times that of oxygen, hence the rapid assimilation and poisoning. The combination is easily broken and in the air or oxygen the carbon monoxide quickly diffuses out, if respiration is deep and continuous, leaving the blood unaltered. Carbon monoxide in itself is not a tissue poison as tissues continue to grow in an atmosphere of 79 per cent. carbon monoxide (Haggard). The asphyxiation from lack of oxygen causes most of the changes but the benzoles in illuminating gas may contribute some toxic action.

Symptoms.—Exposure to a high percentage of carbon monoxide gas, as about blast furnaces or in a sudden entry into an atmosphere of illuminating gas, may prostrate the victim as if he had been struck. Sayers and Yant[2] stress the fact that exercise, such as walking home after exposure may precipitate severe symptoms, even unconsciousness, from the extra oxygen demand. In other cases pressure and throbbing in the temples, weakness of the knees, muscular twitching, epigastric distress with nausea and vomiting, severe headache, ringing in the ears, blurring of the eyes and palpitation are remembered by the patient as some of the symptoms preceding his coma. Inability to move the muscles accounts for many deaths in cases in which a window or door has seemed easily accessible. Hospital admissions for carbon monoxide poisonings usually show coma of varying depth and as the majority have been overcome in sleep they have but a limited range of symptoms. If they recover from the coma they are usually conscious of severe headache or of nausea, weakness, or pains in the muscles. Mental confusion is often in evidence for a few days. Apfelbach states that coma lasting for forty-eight hours is usually fatal. Not uncommonly serious symptoms appear after a

[1] See illustration in W. G. MacCallum's *Text-book of Pathology.*

[2] *Serial No.* 2476. *Dept. of Interior U. S. A. Bureau of Mines. Dangers and Treatment of Carbon Monoxide Poisoning.*

patient has apparently recovered; these symptoms may be in association with the cerebral lesions and appear as psychoses, paralyses, tremors or gross movements, or they imitate closely a peripheral neuritis, though it is probable that some signs of central degeneration will be in evidence. Wilson and Winkelman[1] report 3 such cases. Much has been written on the psychosis subsequent to carbon monoxide poisoning and it is to be remembered that actual degeneration of the brain tissue may have occurred. One of the Toronto General Hospital patients remained disoriented for three months and died shortly after his admission to an asylum. Pneumonia and bronchopneumonia may develop during the comatose period, though pneumonia occurred only in 2 of 32 coma cases in the Toronto General Hospital. Pulmotors or lung motors may be responsible for some of the pulmonary complications. Thromboses of peripheral arteries have been frequent, and gangrene of the skin or extremities may be due to this. Carbon monoxide in any mixture may give rise to the cherry-red color of lips and blood; the pink-red spots are of erythematous nature and bright petechiæ may occur in the skin. There is frothing at the mouth. There may be a strabismus; convulsions have been reported; both increased and diminished reflexes are recorded in coma cases and the presence of a Babinski reflex has been frequently noted. There is no fixed type of respiration; Cheyne-Stokes, stertorous, rapid irregular or gasping, are noted in fatal cases. Moisture is usually to be found in the lungs, possibly from irritation from aspirated secretions; signs of pneumonia or bronchopneumonia require some hours to develop. The pulse and heart beat are weak and often irregular, and fibrillation took place in 1 case investigated; the blood-pressure may be low. There is but little change in the blood count; a high blood sugar is evidently not uncommon though transient; glycosuria occurred in 2 of 32 cases of carbon monoxide coma which the writer has analyzed. Hyperpyrexia may occur; 108° F. was recorded in 1 case and pneumonia or cerebral hemorrhage must be suspected in such instances. The blood when drawn may show the pink-red color but the absence of the color is no proof that carbon monoxide has not been inhaled. Albuminuria and casts are occasional findings and a non-protein nitrogen of the blood of 104 was found in 1 fatal case.

Diagnosis.—This is often a matter of history of exposure to carbon monoxide. The red color of a comatose patient should be suggestive and the color of the blood is confirmatory. There are many tests for the presence of carboxyhemoglobin, the combination in the blood. Hoppe-Seyler recognized the special spectroscopic picture in 1865, two absorption bands in D and E. Wetzel's test requires the diluting of the blood with water in proportions of 1 to 4 and the shaking of the mixture with 3 times its bulk of 1 per cent. tannic acid—normal blood turns dirty gray, carbon monoxide blood remains red. Rapid deep breathing and Cheyne-Stokes respiration may be taken as indicating that the respiratory centre is feeling the lack of oxygen; it results in removing carbon dioxide from the blood. Eventually the respiratory centre fails

[1] *Jour. Am. Med. Assn.*, June 3, 1924.

for lack of its proper stimulus and shallow feeble respiration may be taken as meaning later stages of poisoning with anoxemia and carbon dioxide deficiency. The coma of alcohol, drugs, brain lesions, heart or renal disease must not be overlooked; the various tests for the percentage of gases in the blood are of great value in this connection.

Prognosis.—The depth of the coma and its duration are the important elements; half the patients poisoned recover on the journey to the hospital. If the blood has reached 80 per cent. saturation with carbon monoxide death will probably ensue. No severely poisoned patient is free from the possibility of the development of late cerebral, nervous or arterial accidents, or of the earlier severe pulmonary infections. The treatment with carbon dioxide has materially altered the outlook: of 13 comatose patients treated with carbon dioxide inhalations 2 died, of 19 such cases treated in earlier years, by general methods only, no less than 9 died. Apfelbach states that a coma of forty-eight hours is usually fatal. The psychoses and the neuritis are usually recovered from but some paralysis may remain and the tremors may be persistent. A long continued weakness with neuro-circulatory asthenia often follows the severe poisonings.

Prophylaxis.—In industries much has been done to protect the workers. The instructions issued by the British factory inspectors should be consulted. In homes a watchful eye should be kept on the method of heating, lighting and cooking; gas-stoves with no provision for fume removal should not be permitted. An atmosphere is harmful when it contains 0.02 per cent. of carbon monoxide and dangerous at 0.05 per cent. (Haldane): air can be readily tested by the iodine-pentoxide method. Continued inhalation of air containing 0.2 per cent. of carbon monoxide will cause unconsciousness and death.

Treatment.—After removal from the poisoned atmosphere, artificial respiration by the Schäfer method should be started at once if respiration has ceased or is failing. The use of pulmotors and lungmotors is questionable. Drinker and members of the commission appointed by the American Gas Association consider them dangerous and likely to damage the lungs, if they ever get oxygen down to them; oxygen is useful to replace the carbon monoxide in the blood if the patient is breathing deeply. Yandell Henderson's suggestion[1] that carbon dioxide mixed with oxygen would stimulate the respiratory centre, cause deep breathing and hasten recovery, has been followed by remarkable results: gassed animals that required two hours in air or eighty minutes in oxygen alone to bring the carbon monoxide of the blood down to 10 per cent. have the same effect produced in twenty minutes by the mixture of oxygen and carbon dioxide. In the human cases of gas poisoning, provided the coma has not been of too long duration, the results are equally good. A mixture of 8 per cent. carbon dioxide in oxygen is used or in an emergency the carbon dioxide is given direct until increased lung ventilation is secured by the deep breathing which is produced. The special apparatus for administering the mixture of oxygen and carbon dioxide should be

[1] *Jour. Am. Med. Assn.*, July 1, 1916, August 19, 1916; *Am. Jour. Phys.*, April, 1909 and Henderson and Haggard: *Jour. Pharm. and Exper. Therap.*, August, 1920; *Jour. Am. Med. Assn.*, October 1, 1921; Sayers and Yant: *Report* 865 *U. S. Public Health Reports.*

available for use by gas companies and in hospitals. The return to consciousness depends upon the degree of hemoglobin-carbon monoxide saturation, the length of the exposure to the gas and the damage done to the brain and circulation. Transfusion is not indicated as the blood can be washed clean through the lungs; a long period of rest may be necessary to overcome the weakness and depression which frequently follows poisoning.

Continued exposure to low concentration of carbon monoxide may produce a host of minor symptoms, headache, nausea, vomiting, vertigo, coated tongue, anemia, flushes and palpitation; malaise in a person so exposed should arouse suspicion. The condition is difficult of proof since the blood chemistry has not been confirmative of saturation of the hemoglobin with the carbon monoxide. The steady exposure, the bizarre symptoms and a polycythemia[1] are usually the chief points in diagnosis. The relief of symptoms on removal from exposure has at times seemed to establish the diagnosis in suspected cases.

II. POISONING BY NITROUS FUMES

The peculiar late-appearing symptoms of involvement of the lungs after inhalation of the fumes of nitrogen oxide and nitric oxide were well known to the older pathologists and toxicologists; in Blyth's "Poisons and Their Effects" the interesting details of deaths from œdema of the lungs which had been preceded by no caustic or irritating effects of inhaled fumes are given.[2] Hall and Cooper's study[3] of 20 cases of accidental poisoning and the cases of Wood[4] show how insidious may be the process of inhaling enough of these fumes to produce a fatal result. In both instances firemen in their activities upset carboys of nitric acid on wooden floors or in sawdust; no irritation from the fumes was noted at the time but ten to twelve hours later, 20 men in one case and 8 in the other were in danger of their lives from the sudden and rapidly accumulating œdema of the lungs, and no less than 10 of them died. A destructive inflammation of the lungs with an intense œdema is brought about and the victims die of suffocation. The suggestion is made that the fumes are reconverted to nitric acid on the surface of the bronchi and bronchioles and that the symptoms are due to the escharotic action of the acid. Hamilton[5] describes the cases in the American industries. The similarity of the action of the nitrous fumes to that of phosgene gas ($COCl_2$) used in the late war is striking. This gas decomposes into hydrochloric acid in the lungs and on the mucous membranes and, after a period, in which the absence of symptoms must often tempt the soldier to continue his activities, produces the most intense destruction of tissue with œdema of the lungs. If the man survives the acute œdema he may later succumb to a diffuse bronchopneumonia of an aspiration type. In "The collected studies on the pathology of war-gas poisoning," by Winternitz (Yale University press) the whole question of the effects of the "war gassing" is carefully considered.

[1] Nasmith, G. and Graham, D. A. L.: *Jour. of Phys.*, 1906-7, **35**, 35.
[2] *Lancet*, April 15, 1854; *Chemical News*, March 14, 1863.
[3] *Jour. Am. Med. Assn.*, 1905, **45**, 396.
[4] *Arch. Int. Med.*, 1912, **10**.
[5] *U. S. Dep't. of Labor, Bureau of Labor Statistics, Whole No.* 19.

III. CARBON DISULPHIDE POISONING

Cases of poisoning by carbon disulphide are now seen but rarely, recognition of the danger of exposure having led to better protection. The reputation given to the rubber industry in England, Germany and France was largely due to the unpleasant results seen after the inhalation of the disulphide fumes during the process of vulcanization. Hayhurst's figures, however, dealing with the Ohio rubber manufacturing plants, show that now less than 1 per cent. of 30,000 employees are exposed to the risk of poisoning. Vulcanizing, rubber-cement making, cement tube and can filling and "cold curing" of rubber articles necessitate the greatest exposure; benzine (the petroleum product), is now the substance most used for waterproofing fabrics. Carbon disulphide is still used for degreasing animal and vegetable residues and for making waxed papers; one and one-half parts of the vapor per million of air will produce severe symptoms. Being usually employed with benzol or carbon tetrachloride one must consider the action of these substances in any series of poisonings reported: "rubber poisoning" is a comprehensive diagnosis in the industries (Hayhurst).

Peterson described the first American cases, instances of acute mania and dementia; Jump and Cruice saw acute poisoning in the artificial silk-works in Philadelphia, incomplete removal of fumes from vats containing cellulose, potassium hydrate and carbon disulphide being the cause.

Pathology.—Carbon disulphide poisons largely by its action on the nervous system, entering the body by the lungs and skin. Emaciation, loss of normal fat, and fatty degeneration of muscular tissues and organs are noted in fatal cases. Marked degeneration of the nervous structures results from persistent exposure and a chloranemia is the chief effect produced upon the blood by the steady inhalation of the fumes. No distinctive lesions have been noted in the acute poisonings.

Symptoms and Physical Signs.—Acute and chronic forms of poisoning are recognized. In the *acute* forms, headache, vertigo, palpitation, nausea and vomiting may precede a condition of drowsiness, intoxication, incoordination or even of acute mental disturbances. Convulsions or coma may ensue; hallucinosis is common and the victim is often given to the performance of dangerous impulsive acts. The nervous manifestations are numerous and varied; insanities and dementias are noteworthy sequels; death quickly follows the inhalation of the concentrated vapor.

Cases of *chronic* poisoning have a wide range of symptoms. After a few weeks or months of exposure excitement and a condition resembling acute alcoholic intoxication appear, then faintness, giddiness, exhaustion and headache; the worker becomes irritable and depressed, tastes the disulphide in everything, sleeps badly and is troubled with dreams. He soon shows psychical and hysterical symptoms, even mania, and a general picture of tremulous hyperexcitability. Disturbances of every function of the body are in evidence; perhaps particularly noticeable are nose-bleed, nausea, vomiting, constipation, excessive sexual desire, and in women menorrhagia and miscarriages. Following the period of excitement is one of depression with atrophy, emaciation, pallor, and weakness. Peripheral neuritis, optic neuritis, deafness and loss of knee-jerks indicate

the extent of the neurotoxic action of the inhaled disulphide and all forms of sensory changes are recorded. Progressive mental deterioration sends many of the chronically poisoned victims to the asylum and even a short exposure may induce a psychosis. Prolonged poisoning is usually necessary to give signs of neuritis and paralyses. Apart from the pallor, wasting, tremors and distinct signs of neuritis, such as paralysis, there is little to be found in a search for physical signs; no hemorrhagic tendency is seen and anemia is unusual though a reduction of hemoglobin may be noted.

Diagnosis.—The great importance of realizing that carbon disulphide is to be reckoned with in industrial poisoning is that it has points in common with all the well-known intoxications, and unless it be known that the patient has been exposed to the fumes of this dangerous substance there will be difficulty in distinguishing the symptoms of acute carbon disulphide poisoning from those of aniline, benzine, benzole, carbon tetrachloride, carbon monoxide, hydrogen sulphide, or alcohol. Cases of chronic poisoning may resemble those due to lead, mercury, carbon monoxide or alcohol, and their resemblance to paresis, tabes and progressive muscle atrophy has been pointed out, Hayhurst's description of carbon disulphide intoxication should be consulted in this connection.[1]

Prognosis.—Three of Brius' 8 patients remained demented; Peterson's 3 patients with mania recovered in two years but many remain completely unfitted for further employment. Chronic poisoning rarely results in death. The eye symptoms and deafness are usually recovered from but some paralyses are permanent.

Treatment.—Proper prophylaxis is effective in preventing poisonings. Carbon disulphide may enter the body through the skin as well as by the lungs; in acute poisonings therefore the workers clothes should be removed at once, and his body-surface scrubbed. Oxygen may be used. Artificial respiration should be employed if necessary. A poisoned worker should change his employment. Various lines of treatment will be indicated for the very varied assortment of symptoms and conditions.

IV. BENZOLE (BENZENE) POISONING

In America poisonings from benzole in any number date from the war of 1914–18 when the German supply of benzole and aniline was cut off and plants for the manufacture of these products were erected. Coal tar benzole has come to be used in many occupations in which formerly naphtha and "petroleum benzine" were employed, namely, the solution of rubber, fats, gums or resins. In Germany, benzole has long been known as a very fatal poison to the workman exposed to its fumes. Many fatal cases have been reported in the German trade. A marked increase in the number of cases was seen in England as the increased production of benzole, toluine, amido-benzene, made necessary by the war's demands for explosives, took its toll of workers in the munitions factories.

[1] Hayhurst: In Kober and Hanson's *Diseases of Occupation.*

Selling[1] described the first severe poisoning from benzole in America in girls from a can-making plant using a cement made of rubber and resin dissolved in benzole. Hamilton[2] collected 14 other instances in 1915–16. The Division of Industrial Hygiene of the Board of Health of Ontario found 20 cases of poisoning with 2 deaths 1921–24. Anderson, Boyd and Jackson[3] saw 3 severe poisonings with 2 fatalities in a canning factory near Toronto.

Etiology.—Exposure to concentrated fumes for even a few breaths may be fatal in a few minutes; 0.6 parts of benzole per 100,000 parts of air may cause unconsciousness in two to three hours. A man died from entering a benzene tank which had been emptied, washed with water, steamed out, left for twenty-four hours full of water, washed out twice, boiled for twelve hours and left for ten days with the 16-inch manhole open. The more chronic cases have absorbed benzole in smaller doses from rubber cements, from quick-drying paints, or from the mixtures used to dissolve celluloid, fats, gums or resins, in various industries. Anderson's patients were employed in sealing cans with a rubber-benzole cement and a patient in the Toronto General Hospital had been engaged in japanning. Three weeks to several months may elapse before a worker with benzole may note signs of poisoning; some of the benzole undoubtedly enters through the skin.

Pathology.—Distinctive lesions are lacking in cases of acute fatal poisonings; death ensues from respiratory failure. Benzole has long been known as a leukotoxin and has been used in the treatment of leukemia. Autopsies in cases of slow poisoning show numerous hemorrhages into the skin, tissues and organs, pallor, absence of marked wasting, fatty infiltration of the liver and heart and very characteristic aplastic bone-marrow. The spleen and glands are not regularly enlarged. There is a direct destruction of the leukocytes, platelets, megakaryocytes, and red cells. New cells do not form and there is leukopenia and anemia of high grade; the interference with platelet formation makes an abnormal fluidity of blood. A condition of diffuse fat embolism is described.

Symptoms.—Weakness, dizziness, nausea and headache may precede hemorrhages from the nose, mouth and gums, and the appearance of bluish and purple purpuric eruptions. The hemorrhages may be exsanguinating and free bleeding from the stomach, bowels, kidneys and uterus may take place. A waxy pallor soon develops and symptoms common to the severe anemias are in evidence; although benzole is described as having a specific affinity for nervous tissue there are few signs of gross nervous disease beyond a curious irritability and restlessness. Unless removed from contact with benzole the patients soon succumb. The destruction of the blood may be extreme, platelets may not be seen, the white cells may drop to 4500 per cmm. and the red cells have been found as low as 600,000. The color index is usually normal, nucleated red cells are rare, some variations in the size of the erythrocytes may be in evidence, the neutrophilic leukocytes are reduced in percentage and the mononuclear cells are relatively increased. With the absence of platelets

[1] *Johns Hopkins Hospital Bull.*, 1910, **21**, 33.
[2] *Jour. Am. Med. Assn.*, 1917, **68**, 1445.
[3] *Jour. Can. Med. Assn.*, June, 1923.

there is a marked prolongation of the clotting time of the blood. Tests for fragility of the red blood cells have shown no marked variation from normal. Methemoglobin is more a product of poisoning by benzene derivatives. The urine shows little save as a result of the hemorrhages.

Physical Findings.—The waxy pallor, the fair state of nourishment and the extensive purpuric eruptions make a striking picture; hemorrhages into cavities or tissues may be detected; dyspnœa, rapid heart action and fever are often seen. Subnormal temperatures are recorded.

Prognosis.—The outlook is always grave but the most severe anemia may be recovered from; in one instance of this in the Toronto General Hospital, complete recovery took place although the red cells count had fallen to 600,000 per cmm.

Prophylaxis.—A helmet and breathing apparatus should be worn when entering empty benzole containers; in one American plant white mice are used to prove the presence or absence of dangerous amounts of vapor. The use of benzole should be strictly supervised, more than 1 or 2 parts per 100,000 of air is dangerous and efficient exhaust ventilation is the only protection.

Treatment.—For the less severe cases removal from the source of poisoning may suffice to cure; for the severe anemias transfusions may be the only hope and should be tried. There is no specific medication.

V. POISONINGS BY THE BENZENE DERIVATIVES (TRINITROTOLUENE, DINITROBENZOLE, ANILINE[1])

Many if not most of the benzene derivatives are capable of giving rise to symptoms of severe poisoning, the first named above having poisoned extensively during the war, the two latter are recognized as industrial poisons always likely to be dangerous as they are easily absorbed by the skin as well as by the lungs. Trinitrotoluene poisoned 370 workers in 1916–17 and killed no less than 96 of them; a fatal toxic jaundice was the clinical picture. In dinitrobenzene poisoning, the jaundice is rarely more than a tinging of the skin and scleræ; in aniline intoxication cyanosis is the more evident feature. Acute poisonings from inhalation of fumes or from the spilling of these substances on the clothes may be rapidly fatal from a paralysis of the respiratory centre or from the action of the poison on the nervous system. In the more chronic cases a variety of symptoms may appear. The chocolate color imparted to the blood and the methemoglobinemia produced distinguish all these intoxications. Eventually severe anemia develops with much distortion of the red cells and a marked basophilia. A hyperplastic bone-marrow, a large spleen, fatty changes in the liver and muscles, and the dark chocolate color of the blood are rather distinctive autopsy findings. The chances of recovery depend largely on the severity of the initial symptoms. In *treatment* it is recommended that the clothes be removed and the skin washed in order to prevent further absorption of any poison which might be in the clothes or on the skin.

[1] Hamilton: *Industrial Poisons Used or Produced in the Manufacture of Explosives. Bull. of U. S. Bureau of Labor Statistics, Whole No.* 219, *Industrial Poisoning in Making Coal Tar Dyes, Ibid, No.* 280, *Jour. Indust. Hyg.*, August, 1919; Voegtlein *et al.: Jour. Indust. Hyg.*, 1921, **3**; Davis: *Jour. Indust. Hyg.*, 1921, **3**.

CHAPTER XXIII

ALCOHOL, OPIUM, CODEINE, HEROIN, MORPHINISM, COCAINE

By ALEXANDER LAMBERT, M.D.

ALCOHOL

Etiology.—Young men and women demand release from restrictions and inhibitions to their emotions and drink alcohol to obtain it; older men and women seek relief from their mistakes in life, their misfits of environment, or seek forgetfulness of their misfortunes, disappointments and failures, and use alcohol to obliterate their emotions and memories. Youth, therefore, drinks to enjoy, age to forget. Among Western nations alcohol has been the narcotic sanctioned by custom because its use being bound up with the traditions of hospitality, it has been the easiest to obtain, and its excessive use generally condoned. In the East opium has been the common narcotic used by the mass of people to ease similarly the strains of misfortune and sorrow.

Formerly we believed that a weak will and unstable nervous system was the foundation on which chronic alcoholism or opium addiction was based, now we realize that the will is the conscious psychic energy of the personality, and the direction of its expression is controlled by the instincts and emotions, or intelligence, and only expresses the strength of the resulting determination with which the personality seeks relief from unbearable emotions.

It is the intensity as well as the unpleasantness of the emotions from which relief is sought. It is not a physical craving for drink which irresistibly drives human beings to alcohol, but the various forms of chronic alcoholism, or periodic inebriety, and other narcotic addictions are all expressions of the endeavor of the personality to escape the suffering caused by unsolved psychological problems or unbearable bodily pains.

The intoxication impulse in vigorous youth is the wish to enjoy without restraint and the narcotic forgetfulness of drunkenness is not desired, but comes as a result of excessive ingestion. The intoxication impulse of unhappy youth is the wish for obliteration of consciousness, and of the later years of life, the determination to blot out consciousness, and with it all memory, and sufficient amounts are deliberately consumed to produce the desired effect.

Many physical reasons have been given as causes for alcoholism, when in reality it was the emotional reactions produced by the environment.

Among the poor the weary grind of poverty, with its overwork and insufficient food, causes many to turn to alcohol for relief from the monotony and misery of their existence.

In such families in which drinking is common, not infrequently the children take it at a very early age, and the false idea that alcohol is a tonic and strength producer, causes many people to give it to small children, and lay the foundation of an indulgence that becomes a habit, and chronic alcoholism occurs in youth.

Among the well-to-do many men have drifted into chronic alcoholism because of social demands and the continuous unconscious excesses to which their lives of idleness and pleasure lead.

A not uncommon cause of alcoholism in this country has been the use of patent medicines and nostrums. Many of these contain a very high alcoholic content, and seem to be popular in ratio to this content.

The customs of certain trades lead to alcoholism, but while the demands of modern machinery and electrical devices require a clear mind and steady hands and distinctly tend to produce temperance, the mental wear and tear of other occupations tend to cause an increase in alcoholic excesses. Journalists, artists and physicians are more prone to alcoholism than lawyers, engineers and other professional men, and the weary monotony in the lives of bookkeepers, clerks, accountants and stenographers tends to make them seek relief in alcohol. The exhausting work of stokers and firemen and the irregular hours of the work of stable men and teamsters seem to tend to habits of intemperance.

The difference between the sexes in alcoholism is, that men are more prone to drink to excess for amusement or for forgetfulness, women rarely drink to excess, except for the purpose of hiding or forgetting something which they are unwilling to face.

Heredity has always been said to influence the factor of temperance or intemperance. The physical desire or craving for alcohol is not inherited. The unstable personality which renders an individual more liable to go to excesses, and less able to resist the strain of life, is inherited. Sociological conditions causing emotional excitement, such as labor strikes, cause an increase in the alcoholism in the community among both men and women.

In the communities where alcohol is easily obtainable the curve of excessive indulgence shows a striking difference to that seen in the general incidence of medical and surgical admissions to the hospital. The greatest number of admissions in a hospital for general diseases occurs in the first four months of the year. The greatest number and highest daily average of alcoholic admissions occur during the last four months of the year. The alcoholic curve has also a spring rise, with a summer fall, and then a rise toward the end of the year.

Pathology.—Considering the effect of alcohol on the body, ethyl alcohol is the one chiefly to be considered. In the distillation of whisky other bodies such as aldehydes occur, and some of the higher alcohols, usually grouped under the name of fusel oil, deserve consideration. In the compounding of cheap whiskies and in other adulteration methyl alcohol must be considered.

Methyl Alcohol.—This is also called wood alcohol and is sold in the United States as columbian, colonial, union, or eagle spirits. In Canada, it is sold as greenwood or standard wood spirits. It is used to adulterate

various essences or colognes and often to adulterate cheap whiskies. In experiments on the toxicity of the different alcohols, considering that of ethyl alcohol as 1, methyl alcohol is from 0.46 to 0.8, but this gives a false idea of its true toxicity when taken by man, although idiosyncrasies of resistance to methyl alcohol vary greatly, as the ingestion of 2 teaspoonfuls of it has been followed by blindness; in other individuals many ounces have been taken, followed only by intoxication. Another peculiarity of methyl alcohol is that, except in very large doses, the serious toxic symptoms may be delayed for twenty-four hours or even several days, and the intensity of the poisoning is greatly increased if methyl alcohol is consumed on consecutive days. The only constant pathological change in animals after poisoning by methyl alcohol is fatty degeneration of the liver. In men dead from methyl alcohol poisoning, postmortem examination shows an intense congestion of the stomach and intestines with a characteristic odor of methylated spirits.

Both abroad and in this country there have been published descriptions of epidemics of methyl alcohol poisoning after drinking whisky adulterated with this alcohol. This is not only since Prohibition, but in 1904 and 1905 there were 25 deaths in New York City from methyl alcohol poisoning. Wood and Buller some years ago, published 275 cases of methyl alcohol poisoning, among which there were 122 deaths, and 153 instances of blindness. Stadelman and Magnus-Levy report an outbreak of methyl alcohol poisoning in Germany. All these authors emphasize the idiosyncrasies in the toxic effects, and differentiate the different degrees of poisoning. The mild cases show the ordinary marked symptoms of intoxication with dizziness, nausea and gastro-intestinal disturbance, terminating in perfect recovery in a few days, sometimes followed by more or less serious damage to vision. Even in these mild cases forgetfulness is noticeably marked, and clearness of mentality is evidently lacking, not because the patient is drunk, but because he is not fully conscious. Other patients who seem only mildly poisoned, and in whom the toxic action does not appear until many hours following the ingestion of the alcohol, and in whom mild symptoms are followed by a marked improvement, suffer a relapse after one or two days, and die in the relapse.

Methyl alcohol seems to be broken down in the body at irregular intervals, and there seems to be a great difference in the discharge of the decomposition products, Formic acid may be found in increasing amounts in the urine for four or five days, and the methyl alcohol itself has been found in the stomach contents some days after it has been taken. This is not due to slow absorption after ingestion since in animal experiments it also occurs after intravenous injections. This retarded action remains unexplained. When large amounts of methyl alcohol have been taken, the delayed symptoms do not occur.

In the moderately severe cases, the mentality is more benumbed, and consciousness more clouded; there is marked amnesia, which clears up after recovery, and there is dizziness, nausea and vomiting, with sometimes diarrhœa. The rule in both the mild and the moderately severe cases is that there is constipation, which will not yield to mercurials, but

yields to castor oil. In the moderately severe cases, there is commonly cardiac depression, sweating and a slow pulse; there may be delirium and unconsciousness, which deepen into coma and death.

These patients are subject to attacks of intense dyspnœa, and the dyspnœa is of the type of a diabetic coma with deep full breathing, but which fails to clear up the cyanosis. There is a subjective sense of air hunger, which is very intense. To anyone seeing a patient, and without a history, such a patient gives the impression of cardio-respiratory disease, or a cardio-nephritic attack, or if the patient be unconscious, of an apoplexy. The patient's throat and mouth are hot and dry, and he suffers from an intense thirst. Without any apparent reason, a period of improvement may take place, to be again followed by dyspnœa, and collapse, with death, or the patient may apparently be doing well, have a sudden sharp attack of dyspnœa, and die quickly. Even when the patient is recovering, and apparently doing very well, relapses are very apt to occur. The patient may be so ill that recovery seems impossible, and may yet get well; on the other hand, he may be up and feeling comfortable, when an abrupt attack of dyspnœa may cause sudden death. There is often a sudden development of widely dilated pupils, with complete blindness, or the pupils may be widely dilated, the accommodation being not completely paralyzed, but weakened, After a moderately severe poisoning, dimness of vision increasing to total blindness is the rule.

In the severe attacks of poisoning, an overwhelming prostration. comes on, and the patient sinks rapidly into coma and dies. The majority of deaths from methyl alcohol occur within twenty-four hours, but death may be delayed for one, two or even six or eight days, The blindness may develop in a few hours, or may be delayed for several days. There is often a partial restoration of vision, which may after days, or weeks, changes to complete blindness, with atrophy of the optic nerve. The opthalmoscopic examination shows the visual field contracted, absolute central scotomata, the nerve head first congested, followed by gray or white atrophy and contracted vessels. There are retrobulbar neuritis, papillitis, and atrophy of the optic nerve.

The *prognosis* of methyl alcohol poisoning is very uncertain, mild cases become severe, and severe cases improve from unknown causes. Sudden death in patients that are apparently doing well is common. The *treatment* of methyl alcohol poisoning is most unsatisfactory. Any patient who comes in sufficiently drunk to show a disturbance of mentality, and who does not react to the ordinary cathartics of compound cathartic pills, or some form of mercury, should be suspected of methyl alcohol poisoning, and his urine should be examined to settle the diagnosis. The patient should then be given an abundance of water, and bicarbonate of soda should be pushed by mouth, until the urine is distinctly alkaline, and this should be continued for six or eight days. He should be given castor oil in large doses, and the bowel washed out with high enemata. If an attack of cyanosis and dyspnœa develops an intravenous injection of a 5 per cent. solution of bicarbonate of soda (1 quart, 1 liter), as first suggested by Harris and Benedict, sometimes acts very beneficially. Unfortunately, however, it does not always seem to neu-

tralize the decomposition products of methyl alcohol. At times such an intravenous injection is followed in a few hours by a complete disappearance of the cyanosis, and recovery, even when the patient seemed hopelessly ill.

In some patients, even after such an apparent recovery, the dyspnœa and cyanosis may again return, and another injection may succeed, or fail to relieve them, as the case may be. Too much alkalies cannot be given intravenously without danger to the patient, and while the sodium bicarbonate, 1 quart of a 5 per cent. solution, may be injected twice, once on successive days, it is a procedure not without danger if further continued. For that reason, it would seem best to give the bicarbonate by mouth early, to the patient in whom methyl alcohol has been found in the urine, or in whom there is justifiable suspicion of his having taken it by accident. If there is a suspicion of methyl alcohol poisoning, the stomach should be washed out, as well as the colon.

The alkali treatment seems the only treatment which has given any satisfaction, and it is not always successful.

The treatment of the optic nerve atrophy is not satisfactory in severe cases, although pilocarpine, sweat baths and potassium iodide in the early stages of the disease, as soon as possible, and strychnine hypodermically, seem to limit the extent of the secondary atrophy.

Higher Alcohols.—These, such as propyl, butyl, and amyl alcohol, are undoubtedly more toxic than ethyl alcohol and their toxicity increases as they mount in the chemical scale. This group, with substances such as furfurol, compose what is generally called fused oil. It has often been claimed that these alcohols cause many of the symptoms of chronic alcoholism, but ethyl alcohol is the predominant poison in chronic alcoholism. "In "home brews" and "home distillation" certain ethers go over at lower temperatures into the distillate before the ethyl alcohol begins to distil. Formerly these were discarded and put back into the "mash." They are now retained and cause the rapid intoxicating dissociation of consciousness and subsequent loss of memory seen in many of the cases of acute drunkenness. The home distillation is now also continued after all the ethyl alcohol has gone into the distillate and the higher alcohols are distilled over, which formerly were omitted altogether. They cause the prolonged convalescence, the intense headache, the benumbing and confusion of consciousness, and the utter misery felt during the first twenty-four to forty-six hours of the recovery of many cases of acute intoxication now seen in hospitals. The mortality of these cases is greater than formerly in acute intoxication, the recovery more prolonged, and mental deterioration appears more quickly after fewer sprees. The history these patients give of the short duration of memory between ingestion, and the absolute and complete cessation of all consciousness is very striking. It is claimed that the so-called moonshine whisky, produced in the mountains of some of the Southern States, is very deleterious if drunk when freshly distilled. The fresh rye or corn whisky would contain the greatest amount of fusel oil, for these higher alcohols are oxidized and changed into other substances, which give to old whiskies the various flavors, and the older they are, the less they contain of these

substances. Huss has shown that amyl alcohol, in human beings, taken in doses of $\frac{1}{8}$ to $\frac{1}{2}$ gm., caused no toxic symptoms; doses of 1 to 2 gm. were followed by sensations of oppression in the chest, with temporary feelings of dizziness; doses of from 3 to 4 gm. acted as a gastro-intestinal irritant, causing a burning sensation in the epigastrium, colic, vomiting and diarrhœa. He estimates that the total amount of amyl alcohol contained in 12 to 15 glasses of brandy is only 1 to $1\frac{1}{2}$ gm., and the effect produced by this in ordinary drunkenness would practically be *nil*. Baer studied the effect of adding a definite percentage of these higher alcohols to ethyl alcohol, and found that the addition of 2 per cent. of amyl alcohol caused an appreciable increase in toxicity, and the addition of 4 per cent., a very considerable increase, so that a severe type of poisoning resulted in animals. Furfurol, or pyromucic aldehyde, is also present in fusel oil. Joffroy has found that the toxic equivalent of this substance is 9.14 for rabbits as against 8.20, the true toxic equivalent of ethyl alcohol for these animals. But as a liter of rum contains only 0.015 to 0.04 gm., a liter of cognac 0.005 to 0.015 gm. if we assume that man is as sensitive as rabbits to furfurol, it would require from 300 to 700 liters of rum or brandy to furnish the fatal dose. In old well-seasoned liquors the various substances contained in fusel oil are present in too small quantities to be harmful. The ethyl alcohol, and the amounts of it consumed, and the tolerance or intolerance of the consumer, supply the varying factors in the clinical picture.

Ethyl Alcohol. —This is the main constituent of most alcoholic beverages and to it are due the symptoms of alcoholism as seen in man. Spirituous liquors may be considered as acting in ratio to their alcoholic content; the wines, however, vary in their action, either from the ethers which they contain or, in some instances, so far as digestion is concerned, in proportion to the contained solid matters, rather than to their alcoholic content. The same is true of the action of malt liquors which inhibit digestion through the extractives which they contain and further influence metabolism through their carbohydrates.

It is unnecessary to go into the minute effects of ethyl alcohol on the body or to discuss its action on the various physiological processes. Different individuals show the widest degrees of tolerance and intolerance to the same dosage. Both in its effects on the brain and in the various other viscera the same amount of alcohol seems to produce different lesions, varying in their situation and intensity. With our present knowledge of chemistry it is impossible to explain these variations. What is moderation for one individual is excess for another. It is therefore difficult to define what constitutes the moderate use of alcohol. Duclaux's definition seems the most satisfactory, namely, that alcohol has been taken to excess if an hour after its ingestion one is in any way conscious of having taken it. This is a stricter definition than would usually be considered as necessary to define moderation, but it is a limit within which the drug action of alcohol would not occur and the amount taken would in all probability be burnt up in the body without doing injury. In such moderation alcohol probably does not do more than stimulate digestion and relieve the sense of weariness. Its effect on the circulation

would not go farther than a slight change in the character of the pulse, making it feel fuller and stronger. This is probably due to a dilation of the peripheral capillaries without increasing the pulse frequency and in a slight rise of blood-pressure and contraction of the vessels of the splanchnic area which really produces a change in the distribution of the blood without increasing the frequency of the pulse. If the daily ingestion of alcohol stopped here, probably none of the usual morbid changes would occur. But alcohol is a narcotic and as such generates a desire for more to relieve the relaxation following its use. Some individuals are so sensitive that after a single drink of an alcoholic beverage they are not sober and their intellectual judgment is inhibited, and if their psychologic balance is unstable because of repressions they must then go on to the full indulgence of a prolonged spree. The morbid processes produced by alcohol come under three heads or a varying combination between these three: A degeneration of the intrinsic parenchyma of each viscus, a chronic congestion and degeneration of the bloodvessels, and increased connective-tissue growth or fibroid replacement of the parenchyma. This produces at first a functional disturbance, later a perversion of function, and finally a cessation and obliteration of function.

As concerns the relationship of man to his environment the effect of alcohol on the brain is a predominant manifestation, but for the individual the effect of alcohol on the heart and circulation in acute poisoning and on the heart and abdominal viscera in chronic poisoning is often more important. All the viscera are affected by chronic alcoholism, the cerebral symptoms seeming to predominate only because of the special function of the brain. Death from acute poisoning by alcohol is rare and usually follows large doses in those unaccustomed to its use, or sometimes occurs in children who have accidentally swallowed a large amount of some concentrated alcoholic beverage. The lesions do not correspond to the intensity of the symptoms. The functions of the various organs are overwhelmed so quickly that no anatomical change appears. Death may occur within half an hour or after several hours of drinking, or fatal coma may come on suddenly after several hours. The postmortem appearances, after death from such acute poisoning, show the stomach, the œsophagus, and duodenum often of a deep red color with, at times, punctiform ecchymoses in the gastric mucous membrane. The stomach, or the tissues even, may give out a more or less well-marked alcoholic odor. There may be an acute venous congestion in some of the viscera and the bladder is often greatly distended. There is frequently congestion and sometimes extravasation of blood, or œdema of the brain and its membranes. There may be a serous effusion in the ventricles. In one woman, aged thirty years, previously a total abstainer, who took enormous amounts of alcohol, dying after four days, the brain showed acute encephalitis with marked cellular degeneration. The spinal cord showed degeneration in the posterior tracts and in the cells of the anterior horns. The peripheral nerves were normal.

Microscopically the *nerve cells* show two different lesions. One shows various swellings from varicosities in the course of the protoplasmic processes of some of the nerve cells, associated with partial loss of the

delicate spinous projections normally present. The second change is that of chromatolysis and is shown by the disintegration of the small chromatin granules known as the Nissl bodies, as brought out by the stain of that name. These changes are not in ratio to the severity of the symptoms, as Welch says they do not represent any serious permanent damage to the nerve cells but are rapidly recovered from after the disappearance of the causative factor. These are not general and occur only in the minority of the cells, but have been found in the cells of the cerebral hemispheres, the cerebellum, the medulla, the spinal cord, and the sympathetic ganglia.

Personal idiosyncrasy is as marked in the lesions produced by alcohol as it is in the susceptibility to the same dose. This is true of the intensity of the lesions in any given viscus and in the distribution among the various viscera. In studying the age at which death occurs from chronic alcoholism, there is a noticeable difference between the sexes. Among 541 deaths from alcoholism in Bellevue Hospital, New York, 318 men and 223 women, it is noticeable that the highest percentage of the men died in the same quinquennial period in which there were the greatest admissions, while the greatest percentage of female deaths was ten years later than the period of greatest admissions. Thus 20 per cent. occur in men between thirty-three and thirty-seven years of age and 19 per cent. of the deaths in women occur between thirty-eight and forty-two years of age. This is undoubtedly due to the prevalence of pneumonia at this age. Between thirty-three and forty-two years of age both sexes show practically the same percentage, but there is a very great difference in the number of deaths before thirty-two years of age, the percentage in men being 17.2 and in women 31.4; that is, nearly twice as many young women die of alcoholism as young men. The fact that a large number of young prostitutes are necessarily included accounts for the large number of women dying from alcoholism. To obtain an idea of the lesions in chronic alcoholism, the records of 125 cases were taken from the postmortem reports of Bellevue Hospital, 90 of which were of men and 35 of women. Many histories with pneumonia have been rejected.

In the *heart*, fatty degeneration of the muscle is the most common lesion, brown atrophy combined with fatty degeneration is the second, brown atrophy alone the third, and fibroid myocarditis the fourth. There were often combinations of the above lesions, and while fatty infiltration is said by most observers to be more common than fatty degeneration, the reverse held true in this series. That brown atrophy of the cardiac muscle is caused by alcohol seems to be undoubted, because it was present in one-fifth of the hearts examined in the individuals under fifty-five years of age, considering only those records in which carcinoma and healed or active tuberculosis could be excluded. The secondary effect of alcohol on the heart is shown through the circulatory system and from disease of the coronary arteries we obtain fibroid myocarditis; the enormous hypertrophied heart of beer-drinkers is due to the large amount of fluid. The arteriosclerosis, produced by alcohol or secondary to the kidney lesions produced by it, is also a cause of cardiac hypertrophy and later of the fibroid myocarditis. Sudden death often

occurs in young alcoholics who, possessing a heart with fatty degeneration, further poison it with alcohol, and when some sudden muscular action causes a sudden strain, the cardiac muscle fails, and death results. The arteriosclerotic degenerations show most intensely in the aorta, in the great vessels, and in the ramifications of the abdominal vessels. Cabot claims that general peripheral arteriosclerosis is only seen in 6 per cent. of alcoholics. This may be true, and yet very extensive changes are often present in the aorta and abdominal vessels of patients who show no peripheral arterial changes.

In the *lungs* the lesions found were œdema, congestion, and various forms of pneumonia. It is very common to find tuberculosis in various stages. Pulmonary emboli from cardiac thrombosis and embolism of the pulmonary artery were also found in this series.

In the *liver* the combination of cirrhosis, brown atrophy, and parenchymatous degeneration, with fatty degeneration, was found in 80 per cent. of the men and 74 per cent. of the women. Fatty degeneration combined with cirrhosis was the second most common lesion. Fatty degeneration of the liver is found among those who take large amounts of malt liquors; cirrhosis is usually found in those who drink heavily of wines, whisky, gin, or rum. In this series of autopsies it was present in 48 per cent. of the men and 34 per cent. of the women, and it seems to occur in those persons who, possessing a high degree of tolerance for alcohol, are enabled to consume enormous amounts. It is a noticeable fact clinically that men whose nervous tissues possess a high degree of tolerance are those who find themselves in middle life with cirrhosis of the liver and degenerated viscera. Those who possess an intolerance for alcohol in their nervous tissues are the ones who mentally go to pieces early, and though more often noticeably drunk, less frequently show degeneration of the abdominal viscera.

In the *spleen* chronic congestion and fibrosis were the two most common conditions. Acute congestion occurred next in frequency; other conditions found were brown atrophy, amyloid degeneration, hemochromatosis, and brown atrophy. A very noticeable feature is the frequency with which chronic fibrosis occurs in the *pancreas*. A moderate percentage of fatty infiltration occurred in both men and women and the pancreas was normal in one-fourth of the patients examined. The *adrenal bodies* were normal in a little over one-half of the men and one-third of the women, but in one-third of the men and in over one-half of the women examined there was a fatty degeneration of the cortex.

In this series a very noticeable feature is the fact that there were no records of normal *kidneys*; all examinations showed some lesions, chronic ones greatly predominating. Acute nephritis was mentioned in only 2 men and 1 woman. Acute exacerbation in chronic nephritis was present in 7 men and 1 woman. Chronic parenchymatous nephritis, often with congestion, was the most common lesion, being present in a little less than two-thirds of both sexes. Chronic interstitial nephritis, at times with congestion, occurred in about one-third of the cases. As these examinations were made on patients of from twenty to over seventy years of age who had died from chronic alcoholism, it would seem to show

that while the kidneys for years may escape, sooner or later they are certain to become diseased.

The *stomach* shows various forms of gastritis, chronic gastritis being one of the commonest lesions. An inflamed gastric mucosa, covered with ropy mucus, is common from acute alcoholism and sooner or later goes on into the chronic form. Chronic atrophic gastritis was present in one-half of the cases. Hemorrhagic gastritis was present in about one-fourth of the men and one-eighth of the women. These lesions were not infrequently combined. The mucosa of the intestines does not suffer so much as the gastric mucosa. The most common condition found was congestion, sometimes with œdema. In about 50 per cent. of the patients examined the intestinal mucosa was normal.

The bladder is often overdistended in patients who have died suddenly or had unconsciousness before death. It may be ruptured, as was the case in 2 men in the service of the author. In about one-fourth of both sexes either acute or chronic cystitis was found.

That alcohol tends to produce *sterility* has long been known. In 5 among 12 women between twenty and thirty years of age, the ovaries were markedly atrophic, appearing like those a number of years after the menopause, and in women between thirty-one and forty, they were atrophic in 5 among 8. Thus in 10 of 20 women under forty years of age they showed extensive atrophy. Bertholet has also reported an atrophy of the ovary and ova in female alcoholics. In the men the testicles did not show gross evidences of atrophy, but in the few examined microscopically there was sclerosis. Bertholet found partial or extreme conditions of atrophy of the testicles in the majority of 75 chronic alcoholics. Lancereaux has also proved this, and Simonds observed that in 60 per cent. of chronic alcoholics on postmortem examination azoöspermia was found. Broun and Garnier have confirmed these findings by animal experimentation.

Some individuals will die of various somatic degenerations and still retain apparently normal cerebral tissues, while in others the brain and spinal cord seem to suffer early, and disproportionately, compared with the heart and abdominal viscera. The lesions in the central *nervous system* seem to be brought about either from the degeneration of the cerebral arteries or by the direct action of alcohol on the nerve cells. It is often impossible in any given brain to differentiate the changes due to one or the other of these causes. The membranes usually appear congested with an increase of fluid in the pia arachnoid space. This fluid has been shown by Stillman to be particularly common in alcoholics and to be due to a replacement equalizing the diminution in the size of the brain. This diminution may be due either to the gradual normal diminution in size with age or to an actual shrinkage due to an increase of connective tissue and an atrophy of the cerebral tissues. It occurs more commonly in the chronic alcoholic than in patients dying from other diseases, although it is also found in other conditions. Added to this fluid and meningeal congestion, it is recorded that there was œdema of the cerebral tissues in about three-fourths of the brains of men and about one-half of those of the women examined. Congestion of the cere-

bral tissue was found in 54 per cent. of the men and 14 per cent of the women. Pachymeningitis was not uncommon and pachymeningitis hæmorrhagica is frequently seen in alcoholics, probably from trauma acting on the diseased vessels. All inflammations in alcoholics seem to be prone to the hemorrhagic type and hemorrhagic meningitis was present in three men. The degeneration of the vessels produced miliary aneurisms and it is not uncommon to find recent cerebral hemorrhages, encysted old hemorrhages or areas of cerebral softening from embolism.

Microscopic examination shows an intense degree of atheromatous degeneration of the minute vessels which are enlarged, often tortuous, and unevenly distended with fusiform dilatations. Not infrequently the vessels are plugged and the diseased wall ruptured with extravasated blood and hematoidin crystals in the surrounding areas.

In *delirium tremens* there is a distinct tendency to minute acute hemorrhages which are diffusely scattered in the cerebral cortex in the central and frontal convolutions, less frequent in the cerebellum and still less in the spinal cord. The place of predilection is the region of gray matter around the third ventricle in the aqueduct of Sylvius. These hemorrhages are very commonly observed in the region of the nuclei of the oculomotor and abducens nerves. About the bloodvessels the spider or glia cells are crowded in great abundance. These are densest just underneath the pia and form a thick connective-tissue felting which converts the outer fourth of the cortex into a closely matted layer, much diminished from the normal thickness and often clearly mapped off from the layers beneath. The second and third layers of the cortex show but little change. The fifth layer of motor cells shows extensive fatty degeneration, and, with the spider cells beneath, is undergoing disintegration and absorption. The changes in the spinal cord are similar to those in the cerebral cortex. The vessels of the posterior and lateral columns are more involved than those of the anterior columns. The characteristic change is an obliterating endarteritis, the lumen of the vessel being encroached upon to such a degree that the intima is folded into ridges. At times the vessels are completely occluded. The connective tissue processes from the pia into the cord are thickened, the median raphé of the posterior columns and the peripheral zone of the cord being the areas of election for the sclerotic processes. The anterior and posterior roots are sometimes involved. The degenerative processes may be unilateral or bilateral and the various segments of the cord show varying and irregular degrees of involvement.

In a series of cases of alcoholic *neuritis* in Bellevue Hospital, Harlow Brooks, with whom the work of the author in the pathology of alcoholism has been done, has studied the central nervous system and peripheral nerves. In one patient the peripheral nerves alone showed degenerative changes. The most diligent search with the Marchi method failed to show any corresponding changes in the cord. It is possible, therefore, that alcoholic neuritis may be due to involvement of the peripheral nerves alone, but we believe that this is very exceptional. In some of the other cases there was marked degeneration in the cortical cells of the cerebrum, especially in the motor areas, accompanied by degeneration

of descending fibres in the internal capsule and in the descending columns of the spinal cord; not a true tract degeneration but one of isolated and often widely separated fibres. In the spinal cord extensive cytoplasmic degeneration was present in the ganglion cells of the anterior horn, the ventro-lateral group being especially studied, and there were invariably isolated degenerated fibres in the anterior nerve roots. Degenerated fibres were found in the ascending tracts of the spinal cord, particularly in the severe cases, this being accounted for by alterations, at times very marked, in the ganglion cells of the posterior roots. In some cases ascending and descending degenerations were present in the same spinal cord. Similar results have been found by other investigators.

The pathology of *Korsakow's psychosis* is a combination of what has already been described. This has the dura adherent to the skull, the thickened pia with its gray striations along the course of its vessels, the diffuse cerebral atrophy and increase of the connective tissue, the cellular degenerations shown by Nissl's staining and other changes produced by chronic alcoholism. There is the same tendency as in delirium tremens to small hemorrhages in similar positions as described above. The spinal cord shows degenerations in the various tracts and of the spinal neurons. The peripheral nerves show the various lesions of neuritis or stages of reconstruction.

It is supposed that alcohol reduces the resistance to infectious diseases. This is undoubtedly true in temperate and northern climates. In the tropics, while the statistics from the British army seem to prove the same for India, Major Woodruff gives statistics for the American troops in the Philippines which show that moderate and even excessive drinkers, after two years' residence, were in far better health and more resistant to disease than total abstainers. In the temperate zones an attack of infectious disease in a chronic alcoholic is extremely prone to cause delirium tremens and the prognosis is always grave. Barthelemy emphasizes the fact that waiters and workers around saloons acquire an especially severe form of syphilis. Bärs clearly shows that in epidemics of cholera the disease claims the majority of its victims among the alcoholics and when they are attacked, the chances of recovery are relatively small. In pneumonia the mortality among alcoholics greatly exceeds the average. In Bellevue Hospital in 1904 there were 1001 patients with lobar pneumonia; of these 667 gave a history of alcoholism. Among these the mortality was 50 per cent. and among the non-alcoholics 23.9 per cent.

The results of chronic alcoholism unfortunately do not end with the individual. The children of alcoholics often come into the world as idiots or weak minded and this weak mindedness can be inherited in later generations. Nicloux and Renault, according to Stochard, have shown that alcohol has a decided affinity for the reproductive glands. In the testicular tissues and seminal fluid an amount of alcohol is soon present which almost equals that in the blood of the person having recently taken alcohol. The proportion of alcohol in the testis as compared with that in the blood was as 2 to 3 and in the ovary of female mammals as 3 to 5. The genital glands show as great an affinity for this substance as the nervous system. It must necessarily follow that alcohol may act on the

ripe spermatozoön shortly before the time when it fertilizes the egg, and since an affected spermatozoön may give rise to a defect in the individual, we have a probable explanation for many of the recorded defects attributed to drunkenness at the time of conception. A male in a state of acute intoxication, is more apt to beget an abnormal offspring than is a non-intoxicated male, although a frequent user of alcohol. The experimental data on the sensitiveness of the spermatozoön and the observations on the presence of alcohol in the seminal fluid warrant this statement. Lippich observed 97 children resulting from such conceptions and only 14 were without noticeable defects. Sullivan reported 7 cases of drunkenness during conception which are fairly authentic. Six of the children died within a few months after birth and the seventh was still-born.

Schweighofer has recorded an interesting individual case. A normal woman married a normal man and had 3 sound children. The husband died and she married a drunkard and gave birth to 3 other children; 1 of these became a drunkard, 1 had infantilism, while the third was a social degenerate and drunkard. The first 2 of these children contracted tuberculosis which had never before been in the family. The woman married a third time and by this normal husband she again produced sound children.

That alcohol blights the weaker germ cells in both human beings and animals has been abundantly shown. Demme compared 10 alcoholic families with 10 non-alcoholic families. Only 17.5 per cent. in the alcoholic families were healthy, while practically only 18 per cent. of the non-alcoholic families were not healthy. Sullivan found that from 120 female alcoholics there were 600 children, and of these 335 died under two years of age or were still-born; in more than 60 per cent. of these cases the children died from convulsions. He found that 21 of these alcoholic women had sisters or daughters who were abstinent and who had children from temperate men. These 21 alcoholics had 125 children of whom 55.2 per cent. died before the second year of life, and the 28 non-alcoholic women had 138 children, of whom 23.9 per cent. died before the second year of life. The mortality of children from alcoholic mothers is thus two and a half times greater than from non-alcoholic mothers in these statistics. Animal experiments show the same relative mortality between alcoholic and non-alcoholic animals.

The recent experiments of Stockard with guinea-pigs, continued during thirteen years, confirm the observations of Demme. In these experiments, among the controls the prenatal and postnatal mortality, up to guinea-pig maturity at three months, was 22.9 per cent., and none were physically defective; in the young from normal fathers, mated to alcoholic mothers the death-rate was 43.3 with 6 per cent. defective. Alcoholic males mated with normal females produced young which showed a mortality of 35.1, with 5 per cent. defective. In this mortality of the first generation the prenatal mortality was two and a third times the early postnatal. In the normal control guinea-pigs, the prenatal and the postantal mortalities were equal, In the animals treated with alcohol, the prenatal mortality of the offspring was increased almost eight times more than the postnatal mortality. The damage to the germ cells shows further

in later generations. Among the grandchildren of the treated animals, although their parents had not been directly treated, the prenatal mortality was double the postnatal. Thus the weaker germ cells are eliminated among the grandchildren of alcoholic animals, and the elimination was chiefly exaggerated before birth. Among the animals with the treated great grandparents, the mortality was 40 per cent. higher than among the controls, but those that were hardy enough to survive, produced offsprings of the fourth generation that had a mortality of only 13.5 per cent. against the normal controls of 21 per cent. The elimination by alcohol has thus taken four generations to rid this family of animals of the weakened germ cells; in human beings, this would be one hundred and twenty years. Among savages, and among half-civilized peoples, living without modern hygiene and modern preventive medicine, alcohol probably in the past has eliminated many unfit and weakened germ cells, and of the weakened children produced, it so crippled them that elimination further took place before maturity was reached. Under modern conditions, however, as Stockard points out, under the sociological hygienic and religious influences of civilized life, this elimination does not take place, and the unfit are made to survive and permitted to continue the race. The algebraic sum therefore, of the effect of alcohol on a race, seems to be that it helps to eliminate the weaker germ cells, and to leave after several generations a few hardy individuals, more vigorous than the average, but civilization carries along a large number of individuals weakened and degenerated by alcoholic inheritance, who continue to weaken and further degenerate the race.

Bourneville, in Paris, found that of 1000 idiot epileptics and weak-minded children 471 had a father who was alcoholic, 84 an alcoholic mother, and in 65 both parents were drunkards. In Normandy, Dahl found that 50 per cent. to 60 per cent. of the idiot children had either an alcoholic father or mother. It was noted that in Norway from 1825 to 1835, following the free distillation of brandy, drunkenness was enormously increased and simultaneously the number of idiots increased 150 per cent. Afterward, in the ten years from 1855 to 1865, when the consumption of brandy had greatly diminished, the number of idiots diminished 16 per cent. simultaneously with an increase in the population of 14 per cent.

Bezzola, in Switzerland, studied 70 cases of pronounced idiocy and found that one-half of these idiots were generated during the wine harvest while the rest were divided evenly during the remaining thirty-eight weeks in the year. He further shows that the majority of 8190 idiots were born in the wine districts, and again the season for the maximum birth of such children was nine months after the great national feasts. The normal generation curve of Switzerland showed further that during these same periods of feasting there was a noticeable diminution in the number of children generated.

Epilepsy in children often follows alcoholism in the parents. Spratling mentions that while alcoholism is not usually a direct cause of epilepsy in women, it is frequently an indirect cause through its presence in the parents, nearly always in the father. Kawalewsky, in Krakow,

could prove drunkenness in 60 per cent. of the epileptics. Blueler in Switzerland, could prove drunkenness in the progenitor of 70 per cent. of his epileptics. Congenital deafness and dumbness do not seem to be produced by alcoholism in the parents in any large number of the children with these afflictions. Chronic hydrocephalus seems to be more frequently the consequence of alcoholism in the parents, for, in Berne, 23 of 38 children suffering from this disease had alcoholic parents; in Paris, 18 out of 23 had drunken parents.

Delirium Tremens.—Etiology.—Delirium tremens develops on the foundation of chronic alcoholism. Its occurrence does not run parallel to the amount of alcohol taken, for idiosyncrasy is usually as strongly marked here as in all conditions in which alcohol comes in question. Many men who have never been intoxicated, but who have for years steadily taken alcohol, will, after some severe accident, develop delirium tremens. Its occurrence so far as climate, age, and sex are concerned, is the same as for chronic alcoholism, but it differs essentially in its seasons of greatest frequency and is dependent for its development on other causes, which are engrafted on the chronic alcoholism. It occurs more frequently in northern regions and in the great industrial centres. Where beer and wine are the predominating drinks, delirium tremens is less frequent than in the countries in which men drink spirits chiefly. It has been claimed when the distilled liquors contain less fusel oil there are fewer numbers of delirious cases, The writer has often noticed that delirium tremens patients who had consumed only high-grade whisky, seem to clear quicker than those who had consumed a cheaper grade, but even in these cases the doubt always remains whether or not less ethyl alcohol has been consumed.

The time of year shows a distinct influence on the number of delirious cases. Bonhoeffer, in Breslau, says that the winter months, January, February, and March, show the lowest numbers; from April on there is an increased frequency which reaches its highest point in July and August. The curve maintains almost the same rise through September, and falls rapidly in November and December. The occurrence of delirium tremens in Bellevue Hospital corresponds with the above statements in so far that sudden heat always shows an increase, but there are more patients suffering from delirium tremens during the winter months than in the spring and fall, and the number during the cold months is equal to or even greater than during the hot months. This is due undoubtedly to the large number of pneumonia patients and to the greater number of accidents in the cold months, but even after deducting these, the total remaining is as high among some of the cold months as during any of the hot months. These statements are based on the statistics of 1066 cases. It would seem that the varying occurrence of delirium during various seasons of the year is largely affected by other accidental causes which do not seem to act in different places with even intensity. The previous duration of chronic alcoholism seems to have more influence, and it is said that the average is from six to ten years, although according to Jacobsohn it is never less than seven years. The age at which delirium tremens develops is the same as that in which chronic alcoholism is most

common, that is, between thirty and fifty years. In children it is rare. Bonhoeffer quotes one of sixteen years of age, and the writer saw one boy of fifteen years. It occurs most frequently in men, doubtless because they are more exposed to various accidents, which tend to bring about an outbreak. By some it is claimed that the delirium in women is shorter and less severe than in men; this does not correspond with the opinions of others, although in my experience the delirium in women is usually of a less violent type. It is impossible to say to what extent inherited or acquired mental degeneration influences the occurrence of delirium tremens but that such defect of mental vigor is present in the majority, is beyond question. It seems certain that succeeding attacks of delirium tremens are more easily brought about than the primary one.

Accidental causative factors producing delirium tremens have long been recognized, such as acute infections, trauma, hemorrhage, epileptic attacks, the sudden withdrawal of alcohol, sudden intensity of alcoholic excesses or mental shock. Bonhoeffer, in 250 cases of delirium tremens, could prove in 70 per cent. a recent acute illness or delirium occurring as a complication of it. Undoubtedly the most common acute infection which brings about delirium tremens is pneumonia. Jacobsohn in 281 delirious patients found pneumonia in the ratio of 1 to 8; in 1066 patients in Bellevue Hospital, pneumonia occurred in every fifth patient. Traumatism, such as fracture of the ribs, legs, arms, and skull, very frequently caused an outbreak of delirium tremens, although the percentage in which these occurred is much less than the acute infections. In our experience it is a noticeable fact that severe dislocation at the shoulder or elbow is not so frequently followed by delirium tremens as fractures of the long bones. Bonhoeffer believes that injuries to the breathing apparatus are especially likely to be followed by an outbreak of delirium. Many others lay great stress on epilepsy as a causative factor, but it is a question whether the epileptic seizure is not an expression of the same causative factor which later produces the delirium. An epileptic attack is given as the direct cause of the outbreak of the delirium in from 2.5 to 16 per cent. Among chronic alcoholics, epileptic attacks are very common and in the majority are not followed by an outbreak of delirium. It is difficult, therefore, to accept the view that these are the cause of delirium tremens, although one cannot deny that it is reasonable to suppose that the mental shock produced by them may at times be sufficient to accelerate the outbreak of an already developing delirium. The sudden withdrawal of alcohol in uncared-for patients, in whom no attempt is made to replace it by proper treatment, is at times the cause of an outbreak. This is due to the sudden change of the conditions of life, for when individuals are properly treated, the sudden withdrawal of alcohol does not produce delirium. That delirium tremens is caused by some factor outside of chronic alcoholism seems undoubtedly true, but the definite specific cause is unknown.

Symptoms.—The outbreak of delirium tremens is never sudden; there are always premonitions. The patient becomes peevish, excitable, and restless, loses sleep, and when he falls into slumber, is disturbed by dreams from which he starts in anxious fear. Beginning hallucinations

appear which he recognizes as dreams, but although he knows they are unreal, they still disturb him. He often feels oppression around his heart which may increase to precordial pain; there is singing in his ears, which may develop into voices scolding, abusing, or even threatening him; the dizziness increases; the tremor becomes more marked especially in the hands and tongue. This incubation period may extend over several days or, according to Kraft-Ebing, as long as twelve days. When the delirium occurs in the course of pneumonia it appears generally on the third or fourth day, and, following an accident or fracture, usually on the second or third or may be delayed until the fifth or sixth day. The writer has seen it appear in twenty-four hours, following a severe stab wound in the abdomen. Many patients on the verge of an outbreak of delirium tremens will deny positively and firmly that they have drunk any alcohol; when this is in marked contrast to the physical evidence of alcoholic indulgence it should always warn one of the imminence of a severe outbreak.

Many patients, when they begin to have insomnia and disturbed dreams at night, realize their condition and come to the hospital for treatment. They still know that the hallucinations of sight or hearing are dreams and explain this carefully. Some are still able to focus their attention on other matters and avoid the hallucinations that appear when dropping to sleep. One patient explained to me that he would read most of the night in order to avoid the family of skunks that came and played about his legs. They are often free from hallucinations during the daytime, and after a few nights of disturbed slumber improve, and this abortive form of delirium tremens passes over. In other patients, after the premonitory symptoms, the intensity suddenly increases and they are brought to the hospital in a furious and active delirium. This is usually connected with their daily occupation and they show no fear of what they see but are furiously belligerent; their attention can easily be obtained and they will explain minutely what they see, and demand to have their orders executed and explain logically why they wish to have this done. These patients, after a hypnotic and a night's rest, will clear absolutely and by next morning remember shamefacedly what they had done. The delirium usually does not return.

The majority of patients, when the delirium is fully developed, appear severely ill with a disturbed and anxious countenance or their expression may be one of indifference; the face is congested, often slightly cyanotic and covered with sweat; they are restless, wandering about, busily twisting and turning, listening to imaginary voices and sounds. If in bed, they frequently attempt to leave it, pull and pick at the bedclothes, jump up, attempt to rush from the room and frequently hurl themselves against the walls to escape imaginary objects or push against the walls to prevent their falling in and crushing them. They fail to notice objects in their way and are indifferent to severe injuries. The gait is uncertain from the muscular tremor, which is noticeable in their hands with every movement, and often extends into the tongue and the muscles of the face. Their speech is trembling and stammering, or they blurt out expressions in short, sharp sentences. Some hardly speak at all; others

shriek out questions and answer them, angrily discussing something and frequently scolding and cursing imaginary bystanders. The pulse is full, bounding, and increased in frequency in the young and vigorous individuals and in the elderly or weak it often increases in frequency but is soft and weak. The respirations are increased, the tongue is usually coated, but when the digestion remains good it is often clean, bright red, and glazed; the temperature, as a rule, is near normal. By speaking sharply to the patient, his attention may be arrested for a moment and he may answer the question correctly. Ordinarily the ideas of his personality and past remain clear; but he has false ideas regarding his environment, the purpose for which he is in the hospital, the length of time that he has been there, and the individuals around him.

Hallucinations of sight predominate and it is usually an occupation delirium; for example, an ostler saw innumerable numbers of wagon wheels rolling at him; the circus man saw elephants jutting out into the room, which crowded him, although they did not terrify him; the teamster usually drives horses and it is often a noticeable fact that as long as the horses obey his orders, he is not terrified, but if the horses back against his orders and he is unable to control them, there is terror and the intensity of this is often a fair criterion of the severity of the delirium. Fear is nearly always the dominating emotion in delirium tremens and as here indicated the intensity of this emotion is a rough indication of the severity of the poisoning. The animal or menagerie delirium is common and the patients may see well-known animals, or fantastic beasts, and various horrid forms of monsters, or there may be disgusting insects, crabs, and snakes of various forms. These animals or imaginary monsters are not seen singly but usually in vast numbers. At times the hallucinations are pleasant and the room is filled with beautiful pictures or angels are talking to them. Sometimes the visions take on a sexual type. Various paresthesias of the skin cause hallucinations of worms or spiders crawling on them. Specks on the walls or on the bedclothes may be mistaken for various animals or vermin. Scratches, furuncles, or injuries and the like may be mistaken for the bites of animals or for wounds given in attempts to murder them. The hallucinations of hearing consist of various noises, as the ringing of bells, crying of children, shrieks of people in distress, and volleys of musketry, or they are cursed and jeered at, or they hear their family outside the door conspiring to kill them or whispering and making plans to mutilate them, the mutilations often taking the sexual characteristics. Rarely there are hallucinations of smell, and they imagine that the house is on fire, or that ill-smelling gases are being injected through the key-hole. The hallucinations of taste are also rare, but they may imagine that their food is covered with disgusting substances or that poison is being placed in it. Hypochondriacal illusions from sensations in the intestines, stomach, bladder, etc., do not occur; when present they give cause for the suspicion of other mental diseases. Muscle and temperature sense are normal.

The mental processes are of a peculiar nature; there is no diminution in general in the sharpness of perception of the sense organs; the ability to recognize objects seems intact. Some authors believe that these

patients are unable to obtain any sharp, clear impressions and explain the misinterpretation of noises, etc., as due to disturbances of apprehension; these become very apparent when the patients attempt to read, when instead of correct sentences there is a senseless series of words and sound associations which is especially noticeable when the type is small and indistinct; sometimes there is no relation between the reading and the subject matter. Bonhoeffer's explanation that the inability to read accurately is due to disturbances of attention seems nearer the truth. He believes that the paraphasia and paralexia are closely related to the processes of physiological inattention. The power of attention under special conditions in delirium tremens can for a short space of time attain the sharpness of that in healthy persons, but the ability to hold the attention is quite different. The more complicated the mental work, the greater are the demands on the attention and the greater the tendency to paralexia. With a sharp strain on the attention for the purpose of holding fast this maximum accuracy of any sensory region, a transitory normal value is attained, but there appears an increased tendency to hallucinations in the sensory regions. If the attention is held at a middle level but still so strongly taxed that the patient must talk with and give answers to the examiner, the hallucinations become rarer. The disturbance then records itself in a tendency to mix up words and ideas similar to the physiological inattention. There exists a persistent tendency to sink to a still lower level of attention.

Closely allied to changes in the ability of fixing the attention, is the train of thought by which stimuli through the various sense organs bring about the final conception of the object. Simple pictures presented to a delirious patient, or familiar sounds, may be often correctly recognized and designated, but in severe cases these are often misunderstood and cause hallucinations. At times the misinterpretation of pictures would lead one to believe that lack of color perception played a certain role. It is very characteristic for the misinterpretations to influence and lead to illusions through internal rather than through external similarity, as, for instance, the patient, looking at a picture of a bird declares that it is a bird's nest. The final conception of the objects lacks intensity and the ideas which come into consciousness are those which belong to associated related ideas. These patients are particularly susceptible to suggestion; this, however, extends only to the region of sense from which the hallucinations come, and it is therefore strongest in the optic and in the auditory senses, but often fails with touch, and seems to completely fail in the regions of smell and taste. Suggestion can also affect the hallucinations concerning their external environment, especially as to occurrences in the recent past, but has no effect whatever upon the events of their early life. These patients have no idea of the passage of time and the duration of their illness is usually wrongly given; the day, the week, the year, are ordinarily misstated. The power of retention is much diminished and memory of objects seen is defective, this being strongest at the height of the delirium but also clearly apparent when the delirium has nearly ceased. The power to combine thoughts is distinctly in abeyance; this is clearly seen when one permits a patient

to read, for he will read spontaneously the greatest nonsense without exerting the slightest critical faculty.

One of the most marked peculiarities is the misconception of place and environment and, up to a certain degree, of time; they have entirely lost their orientation. They are able to remember and describe clearly the contents of their own room; one can sometimes make them clearly appreciate the objects which compose their present environment, and yet they will be absolutely unable to appreciate that they are not in their own rooms and in a hospital. Their occupation, former life, and all ideas that relate to their personality are unaffected. Ideas of grandeur do not occur in true delirium tremens; if they appear, it is the complication of some other psychosis. The emotional attitude depends largely upon the character of the hallucinations and illusions; they may be happy or fearful, they are more often anxious and fearful, and these may rapidly replace each other from time to time. The feeling of anxiety is almost never absent from the beginning; it is first seen as an oppression in the chest or as an external restlessness; this seems to be particularly prominent in patients with dyspnœa. During the height of the delirium the anxiety often diminishes and gives place to a euphoria, so that the patient becomes indifferent even to the hallucinations which previously terrified him, and he may even be amused at the external phantasies that are being worked out and played before him. The motor impulses are in most patients very pronounced. As many patients show occupation hallucinations in some degree, so their movements usually correspond with these. The impulse to speak often corresponds with these movements, but frequently patients will be busily moving about for hours, or lying in bed actively busy in many ways, without saying a word.

The *tremor* from which the disease really takes its name is apart from the motor impulse just described and differs from the ordinary tremor in chronic alcoholism only in its intensity and in the greater distribution. It may be so marked in delirium tremens that the patients totter and are unable to hold themselves erect, or, when lying in bed and suddenly spoken to, it may assume such convulsive intensity as to throw them off the bed. It persists even when the patients are at rest, although by movement there is a great intention increase. The tongue trembles strongly when thrust out and this often causes intense tremor in the muscles of the face. The eye muscles remain free from tremor and the head, as a rule, only takes part slightly. In slight degrees it can be controlled when the fingers are held closely together, but becomes distinctly apparent when they are stretched wide apart. In convalescents, after the tremor has disappeared, it can be felt in the interossei muscles when these are taken between the index finger and the thumb. The speech often shows a distinct ataxia; besides trembling of the voice, there is often also a stumbling over syllables and words, and mispronunciation, which is as apparent in voluntary speech as it is in reading aloud. The handwriting shows some disturbance; besides the tremor, words and syllables are left out and an inability to follow straight lines with the tumbling of words above or below each other is seen. Sometimes in the morning tremor of drunkards, a glass of alcohol will steady the hand, so that the handwriting becomes clearer.

There is a great tendency to sweating and often the slightest exertion brings on profuse perspiration. The tendon reflexes are, as a rule, not changed. The sleeplessness continues throughout the entire extent of the delirium and ceases as the delirious period comes to an end. The temperature is usually near the normal line during the delirium; it is raised in some cases, usually not above 101° F., except in patients in whom the motor impulses are very intense and there is incessant muscular movement. Under these conditions temperatures of 103° and 104° F. are not uncommon, and a temperature of 105° F. is of serious prognostic significance. During the summer months, in periods of great heat in New York, it is noticeable that febrile delirium is most common when the motor excitement is very intense. The patient may pass into a condition of heat stroke, the temperature may rise to 108° F., and the patient die.

During the delirium the pulse runs from 80 to 110 when the heart muscle is in fair condition. With much emotion or intense motor activity, the pulse is correspondingly increased; its quality is usually soft. Constipation is the rule. Several German observers lay great stress upon the frequency of albumin in the urine, with no other signs of nephritis, which disappears after the delirium has ceased. Albumin appears in about one-half the cases in the beginning of the delirium, and in others on the second and third day, it is transitory and may cease a day or so before the delirium or it may last a day or two after the cessation, but, as a rule, is small in amount. Leipmann found albumoses in about 15 per cent. of the delirious patients, and toward the end of the delirium they are found in addition to the albumin. Bonhoeffer quotes Elsholz as having found an increase in the polymorphonuclear leukocytes and a diminution of the mononuclear, but no leukocytosis. In cases of severe delirium the eosinophiles were absent. Finlayson and Karnosh showed that the blood and spinal fluid content did not differ in delirium tremens from that of acute alcoholism. Seven cases of acute alcoholic intoxication, 1 acute alcoholism in a chronic alcoholic, 4 cases of acute alcoholic hallucinosis and 2 of delirium tremens were studied, The urea, uric acid creatinin, sugar and chloride content of the blood and spinal fluid of each were estimated. No constant relation was found between the same constituents in blood and spinal fluid, and no parallelism between physical and mental states on the one hand, and the changes in the chemistry of the blood and spinal fluid on the other.

The duration of an attack in mild cases is two or three days; it averages probably three to five days and may continue for eight or ten days. The cessation of the delirium usually follows a deep sleep which may last uninterruptedly for twelve to thirty hours. Some authors describe this sleep as coming on in the midst of the delirium, but it is usually preceded by a period of weariness and relative quiet. When the patient awakens from the critical sleep he is sensible, the hallucinations have gone, and his orientation is usually complete; his mental condition, however, is not fully recovered; the power of retention is diminished and the ability to combine thoughts is distinctly diminished for a few days. The memory of the recent illness is never complete, but it is accurate for the essentials; it is very rare that complete forgetfulness occurs.

As to the duration of his illness, the patient rarely has an accurate idea, deeming the time shorter than it really was. In general the emotional and fantastic occurrences are better remembered than the ordinary ones, but after four or five days even these lose their distinctness. Often for several days therapeutic measures, which were necessary during the stage of delirium, are remembered and still misunderstood as forms of persecution. In old alcoholics who have had previous attacks of delirium, there is at times a certain appreciation of the disease during the entire delirium and they also show a corresponding clearness as to its occurrences. On the other hand, these same patients are very prone to consider hallucinations as realities and retain these misapprehensions for a long period. In not a few patients there is a recrudescence of the delirium for a few nights, while remaining free of it during the day; any unusual excitement producing mental exhaustion may often during the daytime bring back some of the hallucinations.

Meningeal Symptoms, Serous Meningitis, "Wet Brain."—In all forms of alcoholism, but especially in acute and chronic delirium, a condition sometimes develops which has seldom attracted the attention that it merits. It has often been called alcoholic meningitis or serous meningitis, which is a misnomer, for there is no true inflammatory process and the excessive amount of fluid in the peri-arachnoid space is a transudate and not an exudate.

Stillman has made an extensive study of this condition and has proved that the fluid in the pial œdema of most chronic alcoholics is not *per se* an œdema of the pathological process but in every instance represents the reciprocal of brain shrinkage. He further shows that this fluid produces *per se* no symptoms and that the thickening of the meninges takes place chiefly in the arachnoid and is not to be regarded as representing a true inflammatory process. Although this pial œdema is much more common in alcoholics than in any other condition, it has no other significance than that of brain shrinkage. The postdelirious stupor which intervenes following the acute or chronic delirium of alcoholics is not due, as has generally been supposed, to intracranial pressure and the presence of the increased œdematous condition of either the meninges or the brain, but must in all probability be due to cerebral toxemia produced by the chronic alcoholism or in some way connected with the exhaustion supervening from this condition. It occurs with relative equal frequency in men and women. It usually follows an attack of delirium tremens, though it may develop in any chronic alcoholic after an injury or after a debauch without previous delirium. When it follows delirium tremens the patient, after a few days of delirium, sinks slowly into a semicoma. As Stillman points out, the first symptom to attract attention is that the delirium has changed from an active, noisy type into a low, muttering variety in which the facial expression has changed, the heightened color has given place to a gray pallor and almost cadaveric immobility. The patient usually lies flat on his back with legs extended, the head thrown slightly back, and the unobserving glance directed toward the ceiling toward which the hands reach in a rather characteristic manner, suggestive of rope climbing. They are seldom still for more than a few seconds and

exhibit the weak, wide tremor of cerebral irritation. Their mumbling articulation is in counterdistinction to the muttering of other types of delirium in which the spoken words are more sharply defined, but in this form the labials seem absent as if the patients were unable to use their lips.

The patient is aroused with difficulty, though he still will take food. The pulse is rapid, the temperature remains normal or is slightly raised, but seldom over a degree. The pupils are usually diminished in size. The skin is hyperesthetic, and pressure on the muscles of the arms and legs and over the abdomen causes pain. Conjunctivitis and keratitis often develop. In some patients the condition slowly progresses for several days, in others the effusion increases rapidly, and they sink into a more profound coma from which they cannot be aroused. The arms and legs become stiff, the reflexes are all exaggerated, the neck is stiff, slightly retracted, and attempts to move it cause pain. The abdomen is retracted and the skin and muscles are still hyperesthetic. The lids are closed; the pupils are contracted and react slowly if at all. The tongue is dry and brown, and there is usually incontinence of feces and urine. The pulse is frequent and feeble, and the extremities are cold. He may continue in this condition for several days and gradually die, or improvement may begin slowly, the mind becomes clearer, the neck less rigid, the hyperesthesia diminishes, and recovery follows. Often three or four weeks are required before the patient is really convalescent. Pneumonia, especially inhalation pneumonia, is apt to develop; the temperature may rise to 101° to 104° F., and the patient dies. In 709 cases of delirium in Bellevue Hospital, New York, this condition developed in 108 instances (15 per cent.); of these, 37 recovered and 71 died —a mortality of 65.7 per cent. The prognosis is always grave when the coma and rigidity have become well developed. Dana gives the stiffness of the neck as a useful prognostic criterion; if the patient has not a stiff neck he will recover, but when it comes on, the patient dies.

Prognosis.—The outlook in delirium tremens depends greatly upon whether it is complicated by trauma or infectious diseases, especially pneumonia. In 709 cases of delirium occurring in Bellevue Hospital, there were 143 deaths or about 20 per cent. Of these, 61 died of pneumonia, about 36 per cent. There were 125 cases of pneumonia in these 709 patients, and after deducting these in the 584 remaining, the death-rate was about 14 per cent. Of the 125 cases of pneumonia, 64 recovered, leaving a mortality of 48.8 per cent. In uncomplicated attacks in young individuals the prognosis is fairly good. In the beginning of any attack a guarded prognosis should be given. If the delirium develops into a severe form and the motor symptoms are very intense, the prognosis is correspondingly grave. The so-called moderate drinkers, who develop delirium tremens after trauma, have a bad prognosis—in the experience of the writer about 50 per cent. die. In true delirium tremens, as differentiated from acute alcoholic hallucinosis, the tendency to suicide is unusual. The changing character of the delirium prevents the fulfilment of any transitory morbid train of thought. The premonitory stage, when there is great intensity of painful emotions, anxiety, and unrest, is the

time in which the tendency to suicide is most apt to develop. It is difficult in these early stages to say whether the patient is developing true delirium tremens or an acute alcoholic hallucinosis, so that the statement that in true delirium tremens suicide is rare, remains true.

Treatment.—We must realize that there is no specific and the treatment is symptomatic. Most of these patients have been subsisting, often for long periods, on alcohol, with little or no food. The danger is not in the delirium but in the diseased condition of the heart muscle and vessels and that the gastric mucosa is in such a condition that substances given by mouth may remain unabsorbed for hours, and then suddenly be absorbed and the system be overwhelmed by accumulated doses. This has seemed to the writer the reason of the increased death-rate under the old digitalis treatment. Many drugs have been vaunted, but in a disease in which the critical cessation comes on with sleep, it is really impossible to say whether the sleep was coincident with the crisis or whether there was really any cause and effect in the administration of the given hypnotic. The question whether alcohol should be withdrawn at once or continued is still debated. It is the writer's belief, after trying both methods, basing his judgment on the treatment of several thousand patients by each, that alcohol should be absolutely withdrawn in young and vigorous patients but in the weak and elderly it should be rapidly reduced. First and foremost, all these patients must be treated from the standpoint of those having a degenerated heart muscle and they therefore should be stimulated with strychnine (gr. $\frac{1}{60}$ to $\frac{1}{30}$, gm. 0.001 to 0.002) every four hours or oftener, or by caffeine or camphor, and these are best given hypodermically. Strong coffee or tea can be given in mild cases instead of the pure caffeine. The patient must be given a vigorous purgative, such as compound cathartic pills or calomel. In young, vigorous adults, without any appreciable change in their arteries, who have recently been drinking, an emetic such as copper or zinc sulphate is often an advantage. This should never be given in elderly persons or in those who appear old for their age.

In mild and abortive attacks paraldehyde (℥ j to ℥ ij, 4 to 8 cc.) repeated if necessary in an hour, is all that is necessary to cause sleep from which the patients frequently awaken either clear-headed or with their delirium lessened. In the severer cases, the paraldehyde may be given in double this dosage. Other hypnotics, such as sulphonal, trional, etc., act too slowly, the barbituric acid group acts quickly, but produces an unreasonable, ugly obstinacy the following day making it difficult to obtain the coöperation of the patient. Opium should be resorted to only as a last resort and is especially contraindicated with pronounced arteriosclerosis. Hyoscine (gr. $\frac{1}{125}$, gm. 0.0005) and morphine (gr. $\frac{1}{6}$ to $\frac{1}{4}$, gm. 0.01 to 0.015) hypodermically should only be given to young and vigorous individuals in whom the motor symptoms are marked. Hyoscine alone tends to increase the delirium, especially in women. Often in the severest cases a mixture of hyoscine, (gr. $\frac{1}{100}$, gm. 0.0006) with apomorphine (gr. $\frac{1}{10}$, gm. 0.006) and strychnine (gr. $\frac{1}{30}$, gm. 0.002) will quiet them and give at least a few hours rest. Strychnine and apomorphine, without hyoscine will often quiet very quickly a fighting, struggling alcoholic.

Bromides alone are insufficient and in the hands of the writer have been practically useless. Chloral is one of the best drugs when properly administered; small doses are useless. Lancereaux recommends 30 to 60 gr. doses (gm. 2 to 4); the combination of chloral and morphine is especially advantageous in that smaller doses of each can be given and the mixture is more effective than either singly. The mixture of morphine (gr. $\frac{1}{8}$, gm. 0.008), or codeine, (gr. 2, gm. 0.12), chloral (gr. 15 to 30, gm. 1 to 2) with tincture of hyoscyamus (℥ss, 2 cc.), tincture of ginger ♏x, cc. 0.6), and tincture of capsicum (♏iij, cc. 0.2), and water to (℥ss cc. 15), is very effective and can be repeated at the end of an hour. These hypnotics, while causing sleep, do not necessarily cut short the delirium, but after a sleep of some hours the delirium is often quieter and there is the further advantage of rest for the heart. The writer has used ergot hypodermically in Livingston's solution, which is as follows: One dram of the solid extract of ergot is dissolved in 1 ounce of sterile water and 3 drops of chloroform and 3 gr. of chloretone are added, and the solution filtered; this is sterile and should be given straight into the muscles in the gluteal region or in the deltoid. It should never be given subcutaneously; nor along the thigh where the fascia lata is strong and thick; it produces painful spots. The administration of 30 drops of this solution, hypodermically, every two to four hours, reduces the dilated bloodvessels, lessens the various congestions, and brings about a better equilibrium of the circulation. After it, there is a distinct tendency to a quieter delirium and less need of restraint. The writer has never seen symptoms of ergotism although 30 minims of this solution were given every two hours for ten days or longer. As soon as patients awake they must be given food, best in the form of milk or milk and eggs. This should be given regularly every two or three hours during the delirium but if asleep they should not be awakened for any reason. Often these patients have an acute gastritis with severe vomiting. This is best controlled by giving ℥j (4 gm.) of sodium bicarbonate in 1 ounce of peptonized milk every hour and no other food for twelve or eighteen hours. As the gastritis subsides the milk is increased, the soda can be diminished, and the periods lengthened between feedings, In milder cases of gastritis powders of cerium oxalate gr. 10 to 20 (gm. 0.6 to 1.2) sodium bicarbonate gr. 30 (gm. 2) every one or two hours are of benefit, not only to the local gastritis, but also to the acidosis of starvation often present.

The treatment for the "wet brain" condition should be begun as soon as it is suspected. Strychnine, gr. $\frac{1}{60}$ to $\frac{1}{30}$, and ergot, 30 minims, both hypodermically, should be given every two hours, and caffeine and camphor are also of use. The patient should be carefully fed every two hours with milk, broth, and eggs, and thorough purging is advisable. Alcohol seems to increase the effusion and should not be given. During convalescence, however, a little alcohol in the form of egg-nogg two or three times a day for a few days is often of benefit.

Bonhoeffer recommends that delirious patients should be placed for several hours in a warm bath at 95° to 97° F., and that an attendant should sit beside them so that when they attempt to get out of the bath, their attention can be diverted. He also recommends that one or two

attendants should sit beside the delirious patients and keep them in bed, which is excellent treatment where there are many attendants and few patients, but where the reverse is true in a large, active service, restraint is often necessary. There is no question that these patients should be confined to bed through the entire delirious stage, and in the wilder delirium it is often necessary to restrain them by a sheet tied around their ankles and then tied to the foot of the bed, and by another sheet which goes from the bed up over one shoulder, down through the axilla, across the back to the opposite axilla, up across the shoulder, back to the bed; the wrists, when necessary, can be restrained by a muslin bandage wrapped around over cotton wool which thus prevents abrasions and holds them firmly; sometimes a folded sheet stretched across is sufficient to hold them in bed. The hot, stiff, jacket is essentially bad, as it rigidly binds the patient and prevents the radiation of heat. The question of the isolation of these patients and the permitting them to wander about in a padded room is often brought up; young vigorous persons can be so treated for a few hours, provided the tremor is not too great and the delirium not so violent that they will do themselves injury. We have, moreover, always to consider sudden collapse, and the degree of cardiac degeneration cannot be accurately judged, so that, on the whole, it would seem better to keep all patients in bed during their delirium and not to isolate them. In hospitals, the patients, although in open wards, are but little disturbed by their fellows, especially during their delirium, because they are too much occupied with their own hallucinations to pay attention to the disturbances caused by others.

During convalescence, stomachics, such as capsicum, nux vomica, and ginger, are useful. In the febrile cases a bath is often necessary or the patients are placed on a rubber blanket in bed, and cold water is slapped forcibly upon them from a whisk broom; the impact of the water takes the place of the physical rubbing in the bath. Warm packs have been recommended, but often the resistance made by the patient, and the excitement produced, do more harm than good. Usually eight or ten days after the patient has recovered from his delirium he is fit to go out, and in hospitals his treatment here ceases. If possible, they should go to some place where they may live in the open air with good food and have moderate outdoor exercise. Total abstinence from alcohol is their only hope for future health; for this reason it is inadvisable to give any medicine with alcohol in it. The causative psychological disturbance should be treated as in any other chronic alcoholic.

Acute Hallucinosis.—Acute hallucinosis of drunkards is sometimes called acute alcoholic hallucinosis, acute paranoia, or acute persecutory insanity. It is closely allied to delirium tremens, and there are cases which seem more like connecting links than belonging clearly to either one. The patients are usually younger than in delirium tremens and belong to the better educated classes, while delirium tremens is most common among those who perform manual labor. The tendency of this form of alcoholic psychosis to develop as a concomitant symptom of trauma, pneumonia, and other acute diseases is not so great as delirium tremens. Acute gastric disturbances are the most commonly observed

physical ailments connected with it, and it frequently follows fright and intense anger. In the same patient one attack of delirium has taken the form of delirium tremens and another the form of acute hallucinosis.

Symptoms.—These patients show a predominance of the acoustic type of hallucination, although optic and tactile hallucinations are not infrequently present, but not as prominently as in delirium tremens. There is, in the beginning, the same irritability, easily excited condition, restlessness, and undefined dread as in delirium tremens, but they often show a peculiar sensitiveness to ordinary noises; they are sleepless, their dreams are bad, and they start in their sleep, terrified by an unknown something. This unstable condition may persist for days and then become somewhat better, and a further debauch cause all the symptoms to return and go on rapidly into a full development of the complete psychosis. They are often troubled, at first, with noises in the ears, which develop into the hallucinations of singing, music, shooting, screaming, etc.; finally they are persistently followed by definite voices, which hold their attention constantly at high tension and compel their undivided attention. Frequently they are brought into the hospital by the police because they have fled from the persecution of these voices, or they go to their rooms and refuse to come out or allow anyone to approach. In this early stage, suicide is very common, especially in those in whom the terror is highly developed. The voices are sharply localized, they accompany the patient from behind, creep up at him out of the floor, come to him from a hole in the wall, or seem to be persistently telephoning to him. When he strives to sleep, they come up out of the pillow, from under the bed, and they follow his every movement. These voices have a definite character; they may be the voice of a man, woman, or child, or the clearly recognized voice of some friend, or they may be unmistakably not human, or the voices may seem human and speak in a foreign tongue. The rhythmical character of the hallucinations is quite common and sometimes the patient hears constant repetitions of the last word spoken to him, or the last thought which he has had. As he goes into the street the auditory hallucinations, as in delirium tremens, take on the abusive character, and he hears himself called by name with various epithets added, or accused of various criminal acts. Not infrequently, the patient hears every thought as it occurs to him, spoken out aloud, and he declares that he knows the very spot of the tongue out of which his thoughts are loudly spoken; frequently he hears every movement he makes commented upon by the voices.

Optic hallucinations are present but take a subordinate position; they frequently occur at night and often are the outlandish, terrifying, mixed-up pictures seen in delirium tremens. The sense of touch is less often involved and hallucinations of taste and smell are absent. These patients are not usually disturbed by sensations from the internal viscera; sometimes, however, they seem to form an unimportant part of the hallucinations. When these last sensory regions give predominant hallucinations, there is always a strong suspicion that we are not dealing with a pure alcoholic psychosis, but with a more serious condition. Frequently there is a suspiciously disturbing misconception of all acts that

are performed by others in his presence; he believes that people moving in the street are running together to discuss him; he is suspicious of the patients in the hospital, believes that the motions made by the nurse in handing him his food prove he is about to be poisoned, and misinterprets all therapeutic measures. The idea of persecution does not go farther back than the recent past; his persecutory system is superficial, changes during the disease, and often develops suddenly; ideas of grandeur are sometimes present.

Consciousness is not clouded, and they retain their power to combine thought and their powers of retention. Disturbances in the process of thought, as in delirium tremens, are not present. Most authors seem to believe that their orientation for place, as a rule, remains intact. In the patients who show a type of the disease tending toward the clinical picture of delirium tremens, there is sometimes disorientation especially in the beginning of the attack. Tremor of the hands and tongue, and gastritis, are usually present; the symptoms of neuritis are not uncommon, and other disturbances of chronic alcoholism, such as a tendency to perspire freely, etc., are common, although they are usually less marked than in delirium tremens, perhaps because this psychosis more often occurs in younger individuals. The duration of this disease varies from a few days to weeks. Rarely does it continue more than two months, according to Bonhoeffer. As the patients improve, there are periods in which they seem to be free from hallucinations. Finally, the voices in their ears are recognized as such and no longer produce the hallucinations. The various erroneous impressions improve coincidently with the disappearance of the voices. Wernicke believes, however, that these patients go through a paranoiac stage in some hallucinations in which their systematized illusions persist; however this may be, this stage is evidently of short duration, because the accurate appreciation of their psychic condition often occurs with an astonishing rapidity. They remember their hallucinations and are often proud to write a description of them. Sometimes these patient go from these acute hallucinatory stages into a condition of chronic delirium. There are no known pathological lesions characteristic of this psychosis.

Diagnosis.—Bonhoeffer gives the following differential diagnosis between the acute hallucinosis and delirium tremens: The acoustic region dominates in the hallucinations in hallucinosis, the optic and tactile in delirium tremens; in hallucinosis orientation is retained, in delirium tremens it is lost; in hallucinosis the morbid occurrences are systematized and the patient has the illusions concerning his relations with others; both these conditions are lacking in delirium tremens; the disturbance of retention and the disturbances of memory dependent thereon concerning time and succession, the confabulation, the disturbances of attention and the power to combine thought are lacking in hallucinosis or at least are scarcely apparent. In spite of these differences, transitional forms occur which are likely to cause errors in diagnosis.

Prognosis.—The prognosis as to life, if institutional treatment is available is good, but if patients go through the early stages uncared for, the danger of suicide is great. The liability to death from intercurrent disease

is not great, and the more the clinical picture tends toward the transition type of delirium tremens, the shorter seems to be the duration. Ideas of grandeur seem to tend to a somewhat longer duration. If the paranoiac condition has been prominent, continued alcoholic indulgence is liable to produce permanent insanity.

Treatment.—This is the same as for acute insanity; the tendency to suicide must never be forgotten and constant watchfulness is indicated. The patient should be kept in bed during the delirium; hypnotics should be given to produce sleep as in delirium tremens; especial attention should be paid to the digestion and to frequent feeding; and cathartics are usually necessary. Bonhoeffer recommends frequent warm baths. After recovery the necessity of total abstinence from alcohol must be emphasized.

Chronic Alcoholism.—Many of the forms of chronic alcoholism are described under other diseases, such as cirrhosis of the liver, arteriosclerosis, etc., for here, as in all forms of alcoholism, the idiosyncrasies of the patient are important factors and the form and amount of the alcohol used modify the clinical picture. The amount of alcohol which, consumed daily, will produce the lesions and symptoms of chronic alcoholism varies with the individual; most men who partake of moderate doses dilute their alcohol with large amounts of water and the effect produced is less than when the fluids are taken in concentrated forms. Cocktails contain a high percentage of alcohol and being taken on an empty stomach produce a rapid alcoholic response. Many men take moderate amounts of whisky through long years with apparently no serious effects; many others partake of moderate amounts with their meals and seem to be benefited, and not injured, thereby. It is a noticeable fact that the wine connoisseur rarely becomes a drunkard. As soon as an individual begins to take alcohol for the effect produced, he is in danger of continuing the practice and becoming more and more tolerant; he requires more to produce the desired effect and soon partakes of amounts that necessarily must injure the organism.

Dipsomania or Periodic Inebriety.—In some individuals alcoholism shows itself in periodic crises. This is not a single condition, but is the expression of outbreaks of drunkenness, at irregular intervals due to several causes. In some patients it is only the exacerbation of persistent chronic alcoholism, and although they claim not to be drinking between periods, they really are drinking little by little, and finally go on into the full excesses of a spree. Many of these individuals always hope that they can drink without going to excess; many of them are individuals who know that they cannot drink, and yet against their self interest, against their acknowledged determination, cannot seem to cease from taking the first drink that sets them off. Many of these are men who have suffered disappointments, who feel their lack of success in life, and who really are psychological examples of unhappiness, due to a sense of inferiority, and the physical craving and worry that they claim they have for their drink, is actually the expression of restlessness and nervousness, produced by their unsolved psychological problems.

The great majority of periodic drinkers, both men and women, are the unhappy, misunderstood misfits in life, or those discouraged by great

sorrow, to whom life has brought bitter disappointments and disillusionment of their hopes and their ideals, and who cannot face the reorganization necessary to their existence, and who periodically are overcome in such manner that they cannot face their bitter unhappiness. These form the great mass of periodic drinkers. In some men regular recurring mental strains of overwork will bring on an attack of periodic excesses, because they are intolerant of alcohol, and cannot resist the excessive drinking when they once take a single drink. It has often been claimed that these periodic drinkings are similar to periodic epileptic explosions, but the more one sees of these patients, the less does one accept this explanation. The more one sees of these patients, the more one is convinced that the mental depression, the restlessness, irritability, headache, anorexia, sleeplessness, and precordial anxiety shown by these patients, until their desire to drink is irresistible, are but the physical expressions of the underlying known or unknown psychological causes. Many of these patients do not know, or are not conscious of what the compelling emotion is that drives them to these periodic attacks of drunkenness. In some women the time of greatest danger is during their menstrual period. This is particularly true of women whose controlling reason is unhappiness in their marriages, or unhappy love affairs.

A not uncommon cause of periodic inebriety is chronic tobacco poisoning, and this is especially true among the cigarette smokers, Among these patients their alcoholic attacks seem to be without exciting cause, but if questioned closely, one obtains the history of incessant smoking and excessive smoking; this finally makes them nervous, they then smoke some more to quiet their nervousness, which increases under the excessive use of tobacco, until finally they seek another narcotic to quiet them, and naturally turn to alcohol. They are abnormally intolerant of this narcotic, and often after a single drink will not be sober, and then will drink to excess. When recovering from their spree, they will cease to smoke, but after a while when recovered, they begin their smoking again, and the cycle is repeated.

Another common cause of periodic drinking is the recurrent attacks of manic-depressive psychosis, or other psychoses, and these patients only drink when the attacks of the psychosis occur. Among these patients the excessive drinking is not usually the first sign of their manic exaltation. These patients usually begin with an excessive sexual debauch, and begin drinking as the manic exaltation begins to diminish, and they take the alcohol to keep up their feeling of ecstasy. If they begin with a depression, instead of an exaltation, they drink to overcome the overwhelming sense of depression. This form of periodic drinking was but little recognized in the past, but it is becoming more and more recognized as of common occurrence.

For the recurrent attacks of manic-depressive psychoses, institutional care until the period is passed, is the only treatment.

Those poisoned by tobacco should be treated for the relief of the tobacco and the alcohol together, but there is no alternative for these people, they can neither smoke, nor drink. If they begin with either one, they are sure to go to excesses in both. They are so constituted chemically

that they are intolerant to these narcotics and abnormally small doses so poison their nervous tissues, that total abstinence is their only temperance, and no deviation from this strict rule is safe for them.

With the greater mass of patients who are suffering from psychological lack of balance, they must be treated by the solution of their individual problem. They may need institutional treatment, they may not, they all need psychological reorganization, either by psychoanalysis, or by some other method, that will produce the results of giving them an intellectual control of their emotional balance. It is only through control by the intellect over the memories connected with their instincts and their emotions that these patients can live without narcotism. It is not a question of lack of will, it is a question of excess of emotions.

Chronic Alcoholism.—Many men drift into chronic alcoholism unconsciously. Alcohol has been connected so intimately with the customs of hospitality, and of good fellowship, that the ordinary demands of social existence have caused many young men to drift unconsciously into daily excessive drinking, which sooner or later has become a necessity to them to ease the strain and fatigue of existence, and before they know it, men in the late thirties and early forties, have found themselves seriously poisoned by alcohol.

Bleuler defines a man who against his better judgment continually drinks to excess, when he possesses the insight that makes him know he should leave it alone, and who is not yet sufficiently poisoned to show the symptoms of alcoholism as possessed of an alcoholic mania.

The usual description that chronic alcoholics are slovenly in their habits and have lost their ethical sense, that they cannot be trusted in their statements, and have their finer sensibilities blunted, does not necessarily hold true in the early stages of even pronounced chronic alcoholism.

In the clinical picture each individual varies, but they all agree in the emotional instability shown as the earliest of their symptoms. The loss of self respect and of ethical sense, etc., is a later manifestation. A patient is distinctly poisoned by alcohol when he shows after drinking the excessive touchiness at home to gentle remonstrance for the amount he drinks, when he shows excessive ill-temper, meanness, and unreasonableness in his disposition, when over trifles his loss of self-restraint is excessive. The chronic alcoholic is mean and cutting in his remarks to defend himself in the position he knows to be false, but is unwilling to acknowledge it. The chronic alcoholic begins to be filled with defensive excuses, which contain less and less of truth as the necessity for them increases. The home coming of the man with beginning chronic alcoholism becomes more and more disagreeable and dreaded by his family, although he still to the outside world, remains the same pleasant, genial, agreeable companion. It is difficult for a man's friends to believe how quarrelsome and ugly he is, long after it is evident to those with whom he lives, or among whom he works. The chronic alcoholic frequently cynically hurts the feelings of his family as he leaves them to go to his pleasures to enjoy them with his companions. He may still show great possibilities of deep emotions and be roused to feelings of high ambitions, and have a high sense of

value of emotion in a good cause while among his companions, but he is liable to break out in unnecessary anger, and turn and brutally hurt the feelings of his best friend, because of some good natured, thoughtless joke. He is still capable of good feelings and good impulses, but his emotional instability will reverse these constantly on insufficient grounds into vicious resentments.

With this instability there goes an enhancement of a man's self conceit, and a pronounced euphoria, which prevents him from seeing or feeling any mistakes or misfortunes in their right proportions. Another early symptom is the inability to keep promises. He is willing to promise anything, his own reformation, or stirred by a sudden good impulse, shows a strong determination to reform, and within an hour forgets it all, and because of some trifling discomfort, or mishap, drinks to excess. Others buoy themselves up with the excuse that they can stop whenever they want to, should it hurt them at any time, but the vast majority never stop, because they are unable to do so without help from others. Their instability of purpose grows stronger, and they have no persistency of action in their work, or in their thoughts. They are prone to wander and shift from one position or occupation to another. They become economically inefficient, and are always making the excuses that it is somebody else's fault, or that it is hard luck, or anything else, but that it is their own fault they cannot see. They dodge and shift responsibility on to others for their own unreliability and ineffectiveness. Their judgment progressively deteriorates.

Alcoholics are inattentive and forgetful, they do not hear or see well, and remember badly what they do see and hear. In consequence their inaccuracies are so glaring, they are often accused unjustly of lying, when their inaccuracies are really due to forgetfulness and inattention. The difference between real falsehoods and inaccuracies in alcoholics is difficult to tell, because no alcoholic will ever hesitate to use a lie as a help in time of trouble. Women seldom tell the truth about their drinking; men are more prone to be accurate in this slight particular than women. Alcoholics rarely know how much they do drink. It was best summed up by one patient, "that he drank a great deal more than he said he did, and not nearly as much as his wife thought he did."

Alcoholics become increasingly selfish, and self-centered, and increasingly indifferent to the unhappiness and misfortunes which they bring upon their families. They lose their ethical sense of responsibility to their families, and finally they do become slovenly and untidy in their personal habits, and they are increasingly forgetful of their promises and their engagements; they lose their sense of shame, and their sense of honor. They try to justify their injustice and abuse of their family by increasing harshness and increasing brutality. They show an increasing coarseness in their remarks, in their ideas, and in their actions. A characteristic of chronic alcoholism is the unjustifiable suspicion of sexual infidelity in their marriage partner. Kraft Ebing believes that this is due to a failing desire, and a rapidly occurring impotence. Usually this does not express itself further than in vicious vituperation. It however, may be the excuse of outbreaks in fits of drunkenness, which produce bodily harm, and the

murder of an innocent wife, and children, as the suspected accomplices of their mother.

The exact type of mental deterioration varies in individuals, in some degeneration of memory and judgment greatly predominate, and these seem to be the arteriosclerotic type. There are others that take on a pseudoparetic type with ideas of grandeur, with loss of memory, and with progressive loss of responsibility and ethical values, with unlimited conceits, self-confidence and grandiose ideas. The most dangerous and troublesome type are those in whom the emotional degeneration assumes a paranoid type. They build up ideas of persecution, and defence reactions, they are suspicious and twist everything into ideas of personal persecution toward themselves. They develop intense dislikes and hatreds, which is especially common and noticeable toward the members of the immediate families. This makes these patients particularly dangerous, because under the influence of alcohol, these same dislikes and hatreds are frequently translated into criminal acts, and they are liable without warning, and under insufficient provocation when intoxicated, to injure or kill the wife and children, or anyone against whom they have developed a dislike or hatred.

There is a condition in chronic alcoholism seen in hospitals, which differs from those usually described. It occurs in patients in whom excessive indulgence in alcohol, usually without food, has produced exhaustion with complete mental confusion, and a state of amentia appears which simulates manic-depressive insanity. These various forms of mental degeneration may continue through years, and may end finally in senile dementia, especially the arteriosclerotic type. Unfortunately the degeneration of the intellect does not necessarily produce death, and as long as the heart and arteries hold out, many degenerated alcoholics continue to live a burden and a nuisance to the community. They usually die before dementia is fully developed, because of their liability to trauma, and to intercurrent infectious diseases, or they may die during an attack of delirium tremens, or other psychoses, or from visceral degeneration, or from cerebral hemorrhage.

Alcoholic Trance, Automatism, and Pathological Drunkenness.—In psychopathic, hysterical, or epileptic patients, or following traumatic injuries to the skull, or after sunstroke, alcohol produces disturbances of consciousness which deviate greatly from the ordinary sequences. The same conditions are seen in those who have been injured through the excessive use of alcohol; one of the simplest expressions of this condition is that in which the patients, after much smaller amounts of alcohol than formerly, become drunk and are absolutely oblivious next day to everything that occured. After the first or second drink they may seem to their friends simply to have been drinking and not more than usual under the influence of alcohol, or they may in slightly more pronounced cases, completely lose their orientation, misinterpret entirely their environment, and show an ugly disposition, which was foreign to them with evidences of a high degree of emotional anxiety. More pronounced examples of alcoholic automatism are those in which the patient may start off on a prolonged debauch and at the end wake up in some far-

away city with all occurrences from the time he began until coming to himself quite forgotten. The amnesia is usually complete; sometimes there are faint recollections that he has been recently in certain places; for instance, one patient of the writer remembered taking a drink in Boston and ten days later, having gone through a five days' attack of delirium tremens in Bellevue Hospital, came to himself with complete amnesia of everything which had occurred during the ten days. Another who was drinking and sociably chatting with a friend, with no intention of taking enough alcohol to disturb his sobriety, came to himself five days later while ascending the stairs of a station of an elevated road, and was unable to remember any occurrences of those five days except that he had been in some bath establishment. This man was not an alcoholic, and filled a responsible position, although some years previously he had drunk to excess. Other patients, after a single drink or during a debauch, have been known to start off on long journeys and come to themselves on board a railroad train or a steamer. Others have been known to conduct complicated business transactions shrewdly and successfully, to go into court and conduct successfully a long trial, ending with a prolonged charge to the jury, come home and write out a long legal document concerning the case with perfect clearness and conciseness, and yet when consciousness returned, the amnesia was complete. In some this will occur but once, in others it is of recurrent nature and may be preceded by restlessness and irritability, and after a single drink they regularly go into this state of disassociation of consciousness. In these conditions men have committed forgery, theft, and even murder, without any recollection of them when consciousness returned. Many of these cases belong to medico-legal literature rather than to general medicine. There is no question as to the reality of the total amnesia in these cases, and the responsibility for their acts should be placed in the same category as those of the acutely insane.

Some authors differentiate a pathological drunkenness from ordinary degrees of intense intoxication. Formerly it was described as a condition in which a chronic alcoholic on slight provocation, when intoxicated, would commit crimes such as murdering a child, or his wife, and then calmly give himself up to the police with no apparent remorse for what had been done. This type of drunkenness is more the expression of the chronic paranoid type of poisoning, in which a dislike or hatred is translated into the criminal act, and differs from the description of Bleuler and Heilbronner.

These authors believe that there is a usefulness in the practical separation of some cases of drunkenness into a pathological type. It seems to be a manifestation of excessive rage or fury, or uncontrolled motor manifestations of senseless rhythmic movements, following the ingestion of an amount of alcohol so small that ordinarily it would produce no evidences of intoxication. It occurs chiefly in the neuropathic, epileptic or schizophrenic or following hysteria or cerebral trauma. It occurs after excessive fatigue or exposure to excessive heat or cold, or after severe emotional strain. Even as small an amount of alcoholic beverage as two glasses of beer is often sufficient to provoke an attack. The paroxysms

may begin slowly or suddenly, and be started by a slight disagreement or some trifle, or by no apparent cause; it may follow an epileptiform attack, or may even precede one. Sometimes these patients wake up from a nap in a rage, and are disoriented, and feel themselves threatened, and seize a knife. These patients do not seem to show the ordinary lack of coördination, such as seen in disturbances of speech, or staggering. They are markedly disoriented, failing to recognize where they are, and are dominated by terrifying delusions. They may have the hallucination of sight as in delirium tremens, or in hearing as in acute hallucinosis.

This sudden alcoholic "brain storm" may last for a few minutes, or a few hours, and is nearly always ended by a protracted narcotic sleep, from which the patient wakes with a dizzy head, but usually with a complete amnesia, or with but slight recollection of what has happened.

Bleuler says that this amnesia is not always complete, or appears later, perhaps in the course of the following day, at times only after patients have already admitted having committed a crime.

The *differential diagnosis* is based on the fact of the disturbance of orientation, and the hallucinations followed by the amnesia occurring after the ingestion of so small an amount of alcohol that it normally does not cause any manifestations of intoxications.

Usually restraint of these patients is necessary, talking to them is useless. Bleuler recommends hyoscine and morphine in large doses as the only effective hypnotics. It would seem wise, however, to administer strychnine and apomorphine hypodermically to these patients as sedatives, as possibly shortening the paroxysm.

Absinthism.—Lancereaux described a special form of chronic alcoholism produced by excessive indulgence in absinthe, various liqueurs, and aromatic essences. The substances in the absinthe of commerce he divides into two groups, the convulsive and the stupefying; in the first are absinthe, hyssop, and sennel, and in the second annis, angelica, menthe, and marjoram. Absinthe and annis produce the main symptoms. He divides the clinical manifestations into acute, chronic, and hereditary absinthism. The symptoms in *acute absinthism* come on suddenly; the patient becomes agitated, screams, loses consciousness, and falls; there is a tonic convulsion tending to opisthotonos, followed by a succession of clonic convulsions for twenty or thirty seconds, He then falls back heavily, lies still for a few moments, and regains consciousness. He has no recollection of what has occurred and is astonished that people should be caring for him; this lucid interval is of short duration and is succeeded by similar convulsions lasting for ten or twelve hours. In others the tonic convulsions are followed by clonic convulsions, and the patient throws himself from side to side, grinding his teeth, screaming and foaming at the mouth, trying to bite those around him, striking his chest, and tearing at it. These attacks are of short duration and followed by a period of calm; they end suddenly without cyanosis or coma. A series of such convulsions leaves the patient weary and somewhat stupid. For a day or two he may feel the effect but at the end of this time he is entirely recovered. Acute poisoning of this kind is usually recovered from, although death may occur during the attack.

Chronic Absinthism.—The patient not only suffers from convulsive attacks, but also has neuritis and terrifying hallucinations. Chronic poisoning develops often from an indulgence of less than a year and from amounts of the liqueur which seem inadequate to account for the symptoms on the ground of the alcohol consumed. Women seem to suffer more frequently than men, and especially women below twenty-five years of age. These patients have morning vomiting and marked dizziness; there is marked irritability of the muscles; the eyes are fixed and brilliant; they sweat easily; tremor is marked; and there is extreme hyperalgesia of the body. There is marked hyperesthsia of the skin over the exits of the spinal nerves, diminishing in intensity from below upward; the plantar reflexes are extremely active. Pressure on the abdominal wall is painful, and tickling or touching in the lightest way causes such agony that the patient screams with pain. The tenderest points are in the lower abdomen outside the recti muscles and out into the iliac fossæ. This is accompanied, especially at night, by the most intense pain in the muscles of the legs. In cases of long duration the hyperalgesia is succeeded by analgesia, but the pain, on pressure over the abdomen, chest, or the spinal column, remains almost as intense as at the beginning. These patients are sleepless or when falling to sleep are troubled with terrifying nightmares. Hallucinations of hearing are rare, but have a menacing character and are heard especially during the night; the mental ability, as in all alcoholics, shows weakness. One would judge that they lapsed rapidly into the chronic delirium and not infrequently died in this condition.

Hereditary absinthism is shown in children whose parents are addicted to its use. These children seem to possess an unusually unstable nervous system and are especially prone to convulsions in infancy, and later to hysterical manifestations, and convulsive seizures. It has been noticed in Bellevue Hospital during the past years that patients who have given a history of drinking absinthe, have shown attacks of convulsions and in the majority there has been marked hyperesthesia and hyperalgesia of the lower extremities; the extreme types have not come under the writer's observation.

Korsakow's Psychosis.—For many years there has been recognized among chronic alcoholics a condition of delirium combined with a polyneuritis; this was finally classed as a distinct and separate psychosis by Korsakow and is now generally called Korsakow's psychosis or syndrome. Mentally there is loss of orientation and a marked defect in the power of retention of new impressions, and loss of memory for the recent past and also for events during various periods of the patient's whole life. There is a strong tendency to confabulation, and to fabrications of the most absurd character and even hallucinations together with a polyneuritis. This usually occurs in the prime of life and is said by some authors to be more common among women than men, while the statistics of others show a preponderance of men. It usually follows excessive indulgence in alcohol for long periods, although it has occurred as a result of infectious diseases and following poisoning from lead and arsenic. In the majority the psychosis begins with the delirious stage

and this may be so marked that at first a diagnosis of delirium tremens is made, but the critical sleep, so characteristic of delirium tremens, is absent and the delirium pursues a protracted course. Acute hallucinations fall into the background and the defects of mental retention with the lack of orientation of time and space, and the foolish babbling, become more pronounced. In other patients, and some claim this to be the usual course, there is a prodromal period during which there are signs of forgetfulness, mental aberrations, and irritability, in some sleeplessness, and in others a stupor from which they are aroused with difficulty. The symptoms of neuritis may precede the delirium or not come on until after it. The length of this prodromal stage varies in different individuals. Bonhoeffer describes a form which develops as a very slow progressive weakness of memory with a sudden exacerbation of disturbance of memory to a definite standpoint. When, however, the characteristic delirium is developed, there is a distinct loss of memory for the recent past; events of their early life may be very clearly remembered, or up to a certain definite time. This amnesia may be complete or there may be curious lapses of memory in which the patient forgets some events and, without any apparent reason, remembers others which occurred during the same period. Many lose all orientation of time or space; especially is the time element defective; they cannot tell whether an event occurred a few moments or a week or several years ago. These gaps of memory are filled in with curious fabrications. This tendency to confabulate and indulge in pseudoreminiscences is very characteristic.

The sense of recognition is much at fault; the patient does not know those about him, or remember his friends or even his nearest relatives. The attention is easily obtained but kept with difficulty. In the early stages, hallucinations, usually of sight, occur only at night, but as the disease progresses they become more intense and may be present during the day. Optic and tactile hallucinations are most common; these may or may not be terrifying and may assume the fantastic forms seen in acute alcoholic delirium. If the delirious stage comes on early and quickly, these hallucinations are then prominent. The emotional condition varies; some are excited, even simulating a condition of paresis; others are depressed, having the self-accusations seen in melancholia; they are often anxious and disturbed and, later in the disease, are apt to be irritable, quarrelsome, or simply indifferent; in some there is a tendency to be silly and funny; they are at times childish and easily provoked to whining and crying; but in very severe cases they are practically emotionless. They are noticeably lacking in mental initiative and for this reason are very prone to soil themselves; here also weakness of the bodily muscles and the neuritis play a distinct part. They show a distinct power of combination of thought and, as far as the power of retention permits, can reason correctly, especially in some purely intellectual matters.

The symptoms of neuritis are those which accompany polyneuritis; they have the sensory disturbances; there is often an ataxic incoördination; the gait is frequently unstable and they walk with their feet far apart; the regular pains and sensitiveness to touch and muscular weakness

are present; the patellar reflexes are weak or absent; the joints are lax and the muscles soft; these neuritic symptoms are usually more pronounced in the lower extremities and when the paralysis becomes marked, and atrophy quickly follows, there may then be contractions and permanent deformities. Paralysis of the extensors is more frequent than of the flexors. In very severe cases the upper extremities are involved and one finds a radial, ulnar, or median paralysis. Some individual muscles may escape while others may be paralyzed. The sensory disturbances are variously distributed. One can seldom prove these in single nerves but can simply make out well-marked zones of analgesia and hyperesthesia. Disturbances in the sense of position not infrequently occur; delayed reaction to pain has often been observed; ataxia of the upper extremities is often extremely marked. Severe trophic disturbances may occur. The cranial nerves may be affected. The vagi are not infrequently involved, causing cyanosis, tachycardia, and a peculiar dyspnœa which produces short-breathed speech. Double-sided paralysis of the recurrent laryngeal nerves has been observed, as also disturbances of swallowing and of movement of the tongue. Paralysis of the palate has been seen and paralysis of the external eye muscles, especially of the abducens, is especially frequent. Ptosis is not uncommon. Jelliffe draws attention to the frequency with which pupillary disturbances are present. The true Argyll-Robertson pupil may be present, but the pupils are frequently unequal, the reaction may be slow, or there may be paralysis of accommodation. As a rule, the pupils are very small but there may be marked dilatation, especially in the initial delirium. The pupils may be normal and functionate well. Nystagmus has been noted and nystagmus-like twitchings are very frequently seen in the last stages.

Wernicke has described a cerebral psychosis with paralysis of the eye muscles which runs an acute and fatal course; this he called polioencephalitis hæmorrhagica superior. This disturbance of the eye muscles went on to complete paralysis. Wernicke believed this to be a separate psychosis and held that it was characteristic for the clinical picture of the disease to have an associated ocular paralysis, a progressive course, and a rapidly fatal ending. Observations have since shown that patients with this group of symptoms do not always die, and several recoveries have been reported. Bonhoeffer concludes that polioencephalitis hæmorrhagica superior is not a separate clinical entity but that the ophthalmoplegia is moderate in certain cases and is an unusually predominating symptom of a general disease, and he further shows that it is nearly related, if not identical, with Korsakow's psychosis.

The *course* is a protracted one; the first stage up to the full development of the mental symptoms continues for some weeks. The neuritis usually shows improvement before the mental symptoms, and in the course of several months may go on to full recovery, although in some there may be permanent atrophy and paralysis. The mental improvement does not run parallel with that of the neuritis but requires a longer time. The powers of retention seem to be the first to improve; then the orientation improves sufficiently for the patients to recognize where they are,

and they begin to realize who the persons are with whom they come in contact. The length of time during which this improvement occurs is a varying one; it may take months or years before complete orientation has been obtained. Some authors believe that complete restitution can occur; others deny it. Most observers are unwilling to commit themselves to a definite opinion in this regard. Even after apparent recovery, most patients show some weakness of retention and a forgetfulness which often prevents them taking up their former occupations. They are apt to have a distinct lack of initiative and show irritability and unstable emotions while, unless there is total abstinence from alcohol, they soon revert to their former condition. These patients are very apt to die in the delirious stage and in the severe attacks in which the mental symptoms are very pronounced, death is not often long delayed. There is great tendency to die of intercurrent diseases. The *prognosis* in all recent cases is doubtful, and what is of especial importance, it depends upon the general condition of the patient and the state of his cardiac muscle. In the early stages the severer the delirium the worse the prognosis, and when the neuritis extends to the cranial nerves it is especially unfavorable; thus, when the vagus is involved with tachycardia, dyspnœa, and cyanosis, death very frequently occurs. The prognosis for final recovery, if they have passed the severe stages, should always be given with great reserve. Although they may recover a fair amount of physical vigor and of their former mentality, the chances are always in favor of more or less mental defect remaining. Many of these patients seem to recover more of their intellectual abilities than of their emotional values. Superficially they may seem but little changed, but the depths of their personality have been burnt out and destroyed. Their personalities seem hopelessly selfish, and but shallow remains of their former selves.

The *treatment* is in general symptomatic. In the early stages it is carried out best in an institution. In the early months, even in the milder cases, rest in bed is necessary. The neuritis should be treated as any other polyneuritis. The mental symptoms can only be treated through improvement in the general condition. During the severe delirious stages hypnotics may be necessary; in the later stages the milder hypnotics are sufficient when any are needed at all. When the mental condition improves and the patient is able to be about, it is best to give light and easy tasks, which are better than attempts to improve the mental state by special exercise of an intellectual character. When one may be certain that they will receive good care at home and can be reasonably assured of their total abstinence, the patients may be allowed to return to their families.

Treatment of Chronic Alcoholism.—It is not always possible to obtain an accurate history of the length of a debauch or its intensity. If one studies the tremors in connection with the condition of the tongue, in the experience of the writer, a fairly good guess can be made. If the tongue is not coated and there is no tremor, the patient has been drinking about three or four days; if the tongue is moderately coated and there is no tremor, it means the debauch has lasted about five or six days; a heavily coated tongue and no tremor, about seven days; a moder-

ately coated tongue and a slight tremor, about ten days; a heavily coated tongue and a marked tremor, about fourteen days; a moderately coated tongue with a very severe tremor, about three weeks; a fairly clean tongue and a severe tremor, about a month; a bright red, glazed tongue and a severe tremor, from six weeks to three months. This is true of young men up to about forty-five years of age; after that the tremor comes on earlier and a two weeks' spree will give as much tremor in an elderly man as a month's spree in a young man. In women these rules are not accurate; the nervous system is affected more intensely and earlier, while gastritis comes on sooner. A week or ten days' spree brings usually an intense tremor and women will invariably endeavor to hide how much and how long they have been drinking.

The same treatment can be given to a chronic alcoholic as mentioned under delirium tremens. If a patient is furiously and fighting drunk, a hypodermic injection of apomorphine, gr. $\frac{1}{10}$ (0.064 gm.), will quickly transform the most pugnacious into a limp and docile object. He can then be put to bed and will drop off to sleep without further medication. This rarely causes vomiting unless the stomach is full. If it does occur it is of no disadvantage.

Often after a spree the patients feel a disgust for alcohol. But in many of the chronic alcoholics there remains always the nagging desire for it. The following treatment can be given as soon as the patients are manageable: We must clear them of the poison and then endeavor to solve the individual problem either mentally or socially that persistently drives a man to repoison himself. The following treatment will do more to bring a patient to as near a normal condition as possible than any treatment that has as yet come to the writer's notice.

The same belladonna mixture is used as in morphinism (15 per cent. tincture of belladonna 2 parts, and 1 part each of the fluidextract of hyoscyamus and the fluidextract of xanthoxylum). This mixture is given ever hour of the day and night, beginning with 6-drop doses and increasing 2 drops at the end of every six hours until the patients are taking 16 drops, or until dryness of the throat, dilatation of the pupils, or a belladonna rash shows that the patient has reached the limits of tolerance. Some patients can take but little of this mixture, 1 to 2 drops every hour, but as long as they obtain the full physiological effect as judged by belladonna symptoms they obtain the desired results. With the first 6 drops of this mixture from 2 to 5 compound cathartic pills and 5 gr. of blue mass are also given. Five to six hours after this they are given a dose of saline. At about the eighteenth to the twentieth dose of the belladonna mixture they are again given 3 to 5 compound cathartic pills or 5 gr. of blue mass, followed by a saline five hours later, and again at about the thirtieth dose of belladonna mixture the pills or the blue mass are again repeated and again at about the forty-second hour. Often when these last cathartics act, green bilious stools will appear and twelve hours later 1 to 2 ounces of castor oil should be given and the treatment stopped. Sometimes it is necessary to push the belladonna mixture higher than 16 drops to get the symptoms of full tolerance and to obtain the biliary reaction. Sometimes it is necessary to carry this belladonna treatment

over the sixtieth or even into the seventieth hour with extra dosage of cathartics every twenty-four hours as above.

In young vigorous patients who have not been on very long sprees the alcohol can be withdrawn immediately. The general run of patients, however, are more easily treated by "tapering off," and in older or very nervous patients who have been on a prolonged debauch, it is necessary to give 2 ounces of whisky for 4 or 5 doses during the first twenty-four hours. No whisky should be given after thirty hours of treatment. These patients should also have cardiac stimulants such as strychnine and digitalis after the first twenty-four hours, sooner if they are weak. To make these patients sleep, the use of paraldehyde or chloral hydrate and morphine as described under delirium tremens is recommended. If the patient has alcoholic gastritis and is nauseated or cannot retain his medicine, it is wise to give him 20 to 60 gr. of sodium bicarbonate or sodium citrate every hour for 5 or 6 doses. In severe cases the addition of 5 gr. (0.3 gm.) of Tully's powder (pulvis morphinæ compositus) at four-hour intervals for 2 or 3 doses is beneficial. Often the sodium citrate can be given with 10 to 20 gr. of cerium oxalate, if desired. some hours after the Tully's powder has been cut off. If, in the chronic alcoholic, delirium tremens appears during this treatment or following it, it may be necessary to stop the regular treatment and keep the patient asleep with hypnotics, giving him his cathartics once in twenty-four hours and giving abundant nourishment, as milk and eggs. Ordinarily milk does not agree with patients who are taking the belladonna mixture and a light diet of eggs, broths, and bread and butter or a small amount of meat and green vegetables can be given but a milk fermented with lactic acid bacilli does not disagree.

A treatment recommended by McBride, of Toronto, has proved very successful in his hands and has an advantage that patients need not be confined to an institution but can be at home or even at their daily work, coming to the office for treatment. The writer has tried it in a few patients with good results. As soon as the patient is over the severe effect of his debauch or if he is steadily drinking, he should be given hypodermically, three times a day, atropine and strychnine, of each gr. $\frac{1}{100}$ (0.00065 gm.). These drugs should be gradually increased until the full physiological effect of the atropine is obtained and the patient is taking $\frac{1}{30}$ or even $\frac{1}{20}$ of a grain of strychnine three times a day. When the mouth is continually dry and the pupils dilated the atropine should be reduced slightly and held at this dosage for four or five days. Then both the strychnine and atropine should be gradually reduced and finally the patient given the drug twice daily, then once a day, and then stop entirely. The time required is about one month or six weeks. Often the compound tincture of cinchona is added, especially in the morning, when the craving for alcohol is greatest. It is a noticeable fact that after a few days, usually in less than a week, the desire for alcohol has ceased and the thirst from the dryness of the mouth is easily satisfied with water. This has not been universally successful but has succeeded in a large number of patients.

These treatments are really but the beginning stages of what is neces-

sary to help those addicted to excessive indulgence to a permanent regeneration. These drug treatments are the means by which we can eliminate the remains and the effects of the alcohol, and relieve the patient of his nervousness and intense physical craving for the narcotic. To many who have still a vigorous personality, who simply require the opportunity for physical relief from the poisoning which drives them to drink again, this is sufficient and they go on free from their addiction. But these are the exception. Most patients must be treated mentally and physically and be watched and cared for for a year or two before one feels sure that they will not relapse. The best method is to treat the patients physically and build them up thoroughly by as vigorous exercise as their age and circulatory apparatus will permit. Most of these patients are intellectually twisted and their point of view distorted and often perverted; they are the misunderstood, the misplaced, the misfits of society. Sometimes this is only true in their own minds and they have misunderstood their environment. In many, unfortunately, it is really true. Psycho-analysis and mental therapeutics coincident with drug treatment will do more to help these patients than any other form of treatment. They should go to some institution where they can be properly cared for and be built up mentally as well as physically.

The periodic alcoholic can often be reorganized with voluntary rest in an institution, or outside of an institution. But the confirmed alcoholic, who cannot resist the temptation to take alcohol must be persuaded to go voluntarily for a year or two into some institution, or he should be protected from himself by committing him to some institution. When once committed his threats of suicide unless freed, his promises to reform if freed, the suggestion of his friends to give him a chance and let him out, should not be listened to, as his only chance for regeneration is through enforced total abstinence from alcohol.

The poorer masses of society, those that crowd into the great hospitals and alcoholic wards, are unfortunately in no position to obtain this form of treatment. Public opinion has not yet awakened to a realization that these human beings are poisoned and in need of hospital and regenerative treatment rather than jail and punishment. A few States have realized in a measure these facts and through inebriate farm colonies are endeavoring to work out these problems. All social reforms are necessarily slow because to be successful there must be a rearrangement of the public point of view and a growth of new ideas in the average mind. But the regeneration of the mass of alcoholics in a community must be done through the psychological regeneration of the individual and not through the condemnation and punishment of all individuals in a routine mass as is usually done.

OPIUM

Etiology.—The Eastern nations have long used opium to ease the strains of life. The eating of the crude gum and the smoking of prepared opium are the two forms of indulgence in which the drug is taken, and only in recent years in China has the problem of the alkaloids and the substitution of morphine instead of opium occurred in the East.

The problem between the Eastern and Western nations therefore, is expressed differently. In India the natives use opium as the universal household remedy for sickness, as whisky and alcoholic patent medicines are used in the United States. In China and in the Eastern colonies of Western nations, opium smoking is the method of indulgence and public opinion among the natives is not more adverse to this than to tobacco smoking. Of late years the Eastern nations have been taught the use of morphine to replace opium eating or smoking. The Japanese use alcohol and condemn opium, the remainder of the Eastern nations condemn alcohol as a narcotic and condone opium; the Western nations condone narcotism through alcoholism, but they place a moral stigma upon the unfortunate who becomes addicted through pain and disease, to the use of opium or its alkaloids to relieve his physical suffering. The same psychological basis often underlies the use of opium as of alcohol.

In the eastern cities it has been noticeable of late years, where formerly morphine and opium were the forms of opiate addiction, since heroin has come into use, that the vast majority of the heroin takers are below thirty years of age, while the majority of the morphine takers are much older.

In the south, southwest, and west of the United States morphine is still the drug of choice for all purposes.

To what extent the addiction is prevalent in the United States cannot be accurately stated. It is estimated from over 100,000 to over 1,000,000. Kolb and Dumez have calculated on the basis of the amount of opium brought into the country, and legitimately manufactured into morphine that the number of addicts in the country, is 110,000.

Unfortunately there is believed to be a huge mass of opium and its alkaloids smuggled into the country, and the number of addicts supplied by this illegitimate, but very lucrative trade, is impossible to calculate. The number of addicts has unquestionably diminished in the last decade, noticeably the number acquiring the necessity of continuing the habit formed through legitimate medication during illness.

Considering the causes for opium addiction in the United States, a country in which opium taking is against public opinion, and when the habit is acquired, it is in spite of the stigma placed on its addiction, the question often arises as to how many of these patients are driven to this through bodily pain or sickness, how many through psychological disorders, and how many through evil sociological environment.

The statistics given depend upon the source from which they are drawn. Prison and police statistics report 2 per cent. as due to disease, the remainder as due to evil environment. This latter group is composed of many psychopathic individuals, who really belong in the psychologically disordered class, but no differentiation is usually made in this group. The unhappy, and the really vicious are not separated, but are all grouped together, because they have used opiates to balance the emotional values in life between what they hoped to obtain, and what they have been allowed to get.

Hubbard, reporting the statistics of the Health Department Clinic in New York 1919, reported 2469 addicts, of whom 1878 took heroin, 493

took morphine, 4 cocaine, 36 morphine and heroin, 35 morphine and cocaine, and 27 heroin and cocaine. These statistics showed 69 per cent. as due to bad associations, illness 26 per cent., and other causes 5 per cent.

In 1700 patients, with various forms of narcotic addiction in private practice, there are 1135 who took morphine, only 140 who took heroin, 89 took morphine and alcohol, 30 morphine and cocaine, 18 morphine and heroin, 31 laudanum, 19 paregoric, 40 were opium smokers, 9 cocaine, and 11 cocaine and heroin, 17 had the codeine habit, and 1 the dionin. There were various other combinations between veronal, paraldehyde, chloral, with morphine and heroin, Of these addictions 70 per cent. were due to mental or bodily illness, (38 per cent. sickness and bodily pain, 32 per cent. mental strain and psychological disorder), bad associations 22 per cent., and unknown 8 per cent. Bad association was the cause in 14 per cent. of those taking morphine, and in 81 per cent. of those taking heroin; illness in 74 per cent. of those taking morphine, and in 18 per cent. of those taking heroin.

A comparison of the causative factors in relation to the different drugs reveals a noticeable difference in the percentages. Among morphine addicts, 40 per cent. of the men and 25 per cent. of the women took the drug for sickness or indefinite pain, and bad associations claimed only 13.5 per cent. of the men and 8 per cent of the women. Of the 140 taking heroin, 81 per cent. of the men and 70 per cent. of the women took it because of bad associations, but only 6 per cent. of the men and 3 per cent. of the women took it for sickness. Morphine and cocaine addiction was attributed to overwork and fatigue by 32 per cent. of the men; of the women taking this combination, none took it for overwork, but 37.5 per cent. took it because of the pain following operations and an equal number because of bad associations. Of those taking morphine and alcohol 25 per cent. of the men took it for overwork and fatigue, and but 8 per cent. of the women for this cause, Sickness and indefinite pain caused 17 per cent. of the women to seek relief in this combination and but 8 per cent. of the men. Bad associations caused the addictions in but 12 per cent. of the men and 8 per cent. of the women.

There is a strongly marked difference between those whose habit has come through pain, and those who use opiates to smother psychological disorders. The former resent their slavery, and are eager to be free, the latter cling to the drug as their main hope to evade the cruel realities of life. The former use less drug, and struggle against its increase of dosage, the latter steadily creep up in this dosage through fear they will come out from its effects. The former when off their drug relapse only with recurrence of pain. The latter are very prone to relapse.

The only profession or group in this set of statistics from which there were a sufficient number to be judged separately from the rest, was that of medicine, of these 1700, 405 were physicians. It is interesting to compare the causation between physicians and all others. Pain and sickness caused the addiction of 31 per cent. of the doctors, mental strain 16 per cent., overwork and fatigue caused 40 per cent., bad associations 5 per cent., unknown 8 per cent.

Apparently from these statistics one is justified in saying that women more often acquire the addiction of opiates through sickness and pain than men. The mental strain and sorrow, worry and unhappiness are borne about equally well by the two sexes, if anything the men yielding to this cause quicker than women. Overwork and fatigue fall more heavily on men as the usual bread winners, these figures show the great predominance in the break down of the men from this cause. The influence of bad associations is about equal on the two sexes, such environment being slightly worse for the men than the women.

Physicians break through overwork and strain, also during the early years of their professional life, since between the years of twenty-five and forty the addiction was mainly acquired.

Compared with alcohol, opium does not produce such an intense dissociation of personality, nor does it lead to the physical degeneration of the brain. It is not uncommon to see people using opium in some form, in small doses to benumb their overpowering sense of negative self-feeling, or a sense of inferiority. These people cannot face the world and their everyday life, without the benumbing of this curious complex. If they take opiates and bring their ego and its positive self-feeling up to the normal, they succeed in life, and go on through many years of a useful and successful existence. Without it their self-confidence is gone, and they cannot carry on a well-balanced personality. They do not take enough at any time to acquire the deterioration that the average person addicted to the use of opiates shows. It does not destroy their sense of responsibility toward their family, nor to the reaction of the herd instinct in the responsibilities that life brings them. This, however, is true only of morphine and opium. It is not true of heroin. Heroin, as we shall see, damages and annihilates the sense of responsibility to the herd, and removes the sense of responsibility toward others.

Acute Opium Poisoning.—Symptoms.—These require little detailed description; the infrequent, stertorous breathing, the livid cyanotic appearance, the small pupils, the cool, sweating skin, give a well-known and easily recognizable clinical picture. The respirations may simply be infrequent with a rhythmical regularity or they may be in groups of three or four with many seconds between each group.

Treatment.—This is chiefly a struggle to keep up the working of the paralyzed respiratory centre. The old method of walking a patient up and down, injecting large doses of atropine and slapping him with wet towels, has always seemed to the writer ill-advised. The incessant walking up and down, staggering forward and back, half-asleep, exhausts the patient thoroughly and the liability to give, what is for that patient, an overdose of atropine and thereby add its poisonous effects, appears to be a dangerous procedure. One may see patients, brought to the hospital with their hearts very rapid from an overdose of atropine, die suddenly in collapse; they really died from the antidote and not from the opium. The slapping with wet towels soaks them with cold water and in the exhausted condition there is a strong liability that pneumonia may follow. As soon as possible the stomach must be washed out with a solution of potassium permanganate (1 to 500); a certain amount of

this should be left in the stomach; whether opium be taken by the mouth or as morphine, hypodermically, the morphine itself is excreted into the stomach cavity and is then reabsorbed. It has been proved experimentally on dogs that more than one-half of the morphine given subcutaneously can be recovered by simply washing out the stomach. Moor has shown that permanganate of potassium prevents the toxic action of morphine. In opium or morphine poisoning it is therefore wise to wash out the stomach at least every hour and leave a little of the permanganate solution in the stomach to destroy any of the alkaloid that may be excreted by the gastric mucosa. In the periods between washings a strong infusion of coffee should be injected into the bowel. Artificial respiration should be kept up until the patient is able, when let alone, to breathe eight to ten times a minute. This may mean many hours of hard and tedious exertion, but as long as the heart is beating, if respirations are kept up, there is a possibility of recovery. To relieve the cerebral venous congestion produced by opium, the injection of ergot, hypodermically, as described under alcoholism, is most effective and satisfactory. It equalizes the circulation and relieves the congestion.

Opium Smoking.—The smoking of opium is an ancient addiction and compared with the other uses of opium takes longer to form a real habit, works less physical and mental injury, and is easier to cure. A gradual rise in the amount used is necessary in order to get the desired effect; the early pleasurable symptoms soon disappear and the evil effects are similar in many respects to the other forms of taking opium and the symptoms of abstinence are the same. In smoking opium, the morphine is not all consumed and a large amount remains in the ash. Kane gives the tabulated statement of the daily dose of 1000 Chinese smokers; 646 varied between 16 and 128 gr.; 250 from 160 to 320 gr.; 104 from 480 to 1600 gr. To obtain the desired effect 5 gr. seem sufficient for a novice, while old smokers need as high as 290 gr. The average American seems to consume more than the average Chinaman to obtain the desired effect. This method of using opium was first taken up in this country in 1868, in San Francisco; for a time it rapidly spread through the West and from there to the East, but now throughout the United States, owing to the ease of detection and the prohibiture of importing prepared opium for smoking into the United States, it has been largely supplanted by other forms of opiate indulgence.

Symptoms.—The effect of opium smoking on a novice is described by Kane. The first effect was nausea and dizziness, accompanied by a pleasant sensation of exhilaration, followed by a quiet, easy contentment; this was after deeply inhaling four pipes; there was an increase in the force and frequency of the pulse from 80 to 110, hot flushes over the body and face, and after a few more pipes came a soft pulse, lessened in frequency, and a fall in temperature, giddiness, and slight nausea, with some staggering on rising or walking, profuse perspiration, ringing in the ears, and intense itching over the entire body. The profuse perspiration and nausea continued, followed shortly by abundant and easy vomiting; there was also a feeling of uncertainty in putting down the feet in walking, sleepiness, heaviness of the eyelids, contraction of the pupils, dryness of the

throat, and a fear of crossing the street if a wagon or car was approaching. The sexual appetite was increased. This was followed by intense sleepiness. The doze, however, lasted but a moment, the awakening being sudden; there were no dreams. The nausea was a prominent and distressing symptom and, in his case, lasted for twenty-four hours as did also the itching. Sometimes the novice does not feel at all sleepy and becomes very talkative even after the tenth pipe, and later, when desiring to sleep, although sleepy, he is unable to do so from intense fear that some catastrophe may occur. Among other novices the drowsiness comes on after four or five pipes, and they sink back into a heavy slumber, lasting for some hours. Twenty-four hours after smoking, the novice frequently feels languid, is without appetite, has an intense headache, and the itching continues. Old smokers do not, as is usually believed, smoke a few pipefuls and then fall into a heavy sleep; as experience grows into a habit, stupefaction is less speedy, and it may require many hours and many pipes before even the coveted excitation is reached, and the majority complain that they are sleeping less than usual and are troubled by distressing insomnia.

The effect of opium smoking is first seen upon the mind. The feelings of pleasant exhilaration and contented indifference are gradually more difficult to obtain and, after from three months to a year, they cease to occur, although the amount of opium smoked be largely increased. The continuance of the smoking brings with it a disinclination for continued mental effort, a weakness of the will-power, a lack of decision, and a loss of memory. A certain indecision, manifested by mental perplexity and impatience concerning the smallest actions, is often noticed after smoking. During periods of despondency, suicide, especially in women, is not uncommon. Neuralgias, noticed in other forms of opium taking, are rare during opium smoking. Occasionally colic is complained of, but this seems more due to intestinal disturbances than to a direct effect on the nervous system. Tremor of isolated muscles sometimes occurs, but a general tremor, most marked in the hands and tongue, is noticed when smoking is excessive. The pupils, as a rule, are evenly contracted. When the effect of the last dose has worn off, the pupils are often widely dilated, and conjunctivitis, with burning and excessive lacrimation, is common. The pulse-rate is usually above normal, except that after excessive smoking it falls below the normal rate. The flushing of the face with profuse perspiration in a novice is replaced, in the old smoker, by a sallow and deathly hue. When under the full effect of the opium, the respiratory rate is lower and prolonged smoking produces a chronic bronchitis with cough, and pharyngeal and laryngeal catarrh with loss of power in the vocal cords. In the alimentary tract there is gastritis and constipation, often accompanied by hemorrhoids and an obstinate pruritus. The constipation is at times succeeded by a violent diarrhœa, which may become chronic and last for months.

The itching of the skin varies with the individual; in some it is slight and in others intense, especially in the genital region, so that they often excoriate themselves. For the first few months of smoking, in both sexes there is an increased sexual desire which is especially marked in

young women, and opium smoking has been used as a means of seduction. After a few months there is a diminution of desire and impotence in the male. In the majority of women menstruation is not interfered with, although in some it is scanty and irregular, and there may be amenorrhœa. In this, opium smoking differs materially from morphine addiction. Some women who smoke excessively habitually miscarry; in others it seems to have no effect whatever upon their pregnancy, and the children of some opium smokers, so far as can be learned, seem strong and healthy.

The symptoms of abstinence and the sudden cessation of opium smoking are the same in most respects as follow the withdrawal of other forms of opium but the smoker often suffers less severely and for a shorter time. The respiratory tract and the eyes are affected out of proportion to the rest of the body. The first symptoms are gaping, yawning, sneezing, profuse discharge of tears and mucus from the eyes and nose, irregularity of the pupils, ringing in the ears, followed by extreme restlessness, intense pain in the joints, nausea, vomiting, and purging. A peculiar dull, drawing, dry, and burning ache in the pharynx and larynx occurs, which is followed by distressing pains in the muscles, especially in the calves of the legs and between the shoulders. Chills, followed by flashes of heat, are felt along the spine and are followed by profuse perspiration. In some cases, if no opiate is used, the vomiting and diarrhœa continue and the restlessness and flushed face give place to complete relaxation, a gastly pallor with sunken eye, collapse, and death; but in less severe cases or when proper remedies are used, the distressing or dangerous symptoms cease one by one. Sleeplessness persists for a long time; the bronchitis and catarrhal inflammations of the throat usually last for months; the pain in the legs and body gradually disappear; the sexual power returns; the appetite gradually improves and becomes ravenous; an increase in the weight is manifested; a return to natural buoyancy of mind begins, and the patient regains his health and strength. When once cured, it is difficult to say what proportion relapse, but a single indulgence may be sufficient to start them again into the habit. Rarely, individuals are found, who having broken the habit, return to it and smoke but one pipe a week and do so for years without apparent injury.

Opium by Mouth.—This is much more widespread in this country than is generally realized. Probably the most of the opium takers are those suffering from "rheumatism," neuralgias, migraine, hepatic or renal colic, dysmenorrhœa or other troubles which at first caused only a temporary indulgence. Opium is often used at intervals for insomnia or to allay grief and mental suffering. It is given up when the strain is past, and taken up again for any reason that seems sufficient. Often in these cases the only symptoms seem to be a mental and physical restlessness and anorexia, with a disposition to sleep. The opium taker shows certain differences from the individual taking morphine. There is more excitement and exaltation following morphine, while with opium there is more a feeling of quiet contentment, lasting over a long time. The morphinist, after the feeling of satisfaction has worn off, is more apt to dread the slavery of his habit, while the opium taker never seems

fully conscious of the danger. The opium taker rarely consumes as much as the morphinist and the duration of his existence, after the habit is once formed is usually much longer. He may indulge for a year or more without apparent injury, but the morphinist in a relatively short time, shows evidences of deterioration and succumbs quicker.

Gradually the effects of the opium begin to show when used to excess. There is a change in the disposition; the individual becomes irritable, peevish, somnolent, and shows evident dishonesty in little matters, especially concerning the use or the procuring of the drug. A sallow parchment-like complexion is common, although in the early stages the face may be flushed, with a tendency to cutaneous eruption; the hair tends to become gray early and there is an old, exhausted, or cachectic appearance. There is often general feebleness with tremors, and this may be so pronounced as to resemble ataxia. Sometimes the imagination seems stimulated for a while, producing a dreamy, visionary state, but it is extremely doubtful if, under the influence of opium, the mind is capable of more intellectual vigor. There is a tendency to ignore and to break appointments and social engagements. If the opium taker is found in company, it is usually among those who are below him in intellectual and moral development. His self-respect is gone, he is careless of his appearance, indolent in his habits, and neglectful of the decencies of life. In the later stages cardiac degeneration is prone to occur with attacks of cardiac pain or precordial anxiety; constipation is common, and the general nutrition is much disturbed.

CODEINE ADDICTION

The question often arises as to whether or not codeine in itself will produce a habit. In 1700 patients in private practice, this form of opiate addiction was seen in 17, 10 men and 7 women. It was taken more as a pure subduer of pain than for any other reason. The dosage had to be very frequently repeated to obtain any satisfactory results. The narcotic action of codeine in the body does not persist for as long a time as that of morphine and heroin. Nor is it as intense as either. Codeine is practically one-eighth as strong as morphine, and heroin is three times stronger than morphine.

Some people have an indiosyncrasy against codeine, it produces a flushing of the skin, or a fine red rash, with intense itching. In a patient who has recently been broken from a morphine addiction, if codeine is persisted in, it soon brings on a narcotic desire, and because of its insufficient narcotic sensation and emotional value, it is soon disregarded for the morphine, and the patient goes back to his habit.

Codeine does not produce the emotional narcotic value that morphine and heroin do. Moreover, the elimination of codeine is very much quicker from the body, codeine being eliminated from the kidneys unchanged, heroin also is eliminated in this manner, morphine is absorbed, and acted upon by the liver, being broken down into oxydimorphine. It is resecreted by the stomach, and goes out through the bowels. Codeine in medicine is one of the most useful drugs as an analgesic. It is usually quoted as

being less constipating than morphine, the writer's personal experience is that it is more constipating, but in abdominal pain it relieves the pain more satisfactorily than morphine. From its lack of emotional narcotic value, from its shorter action, and necessity of frequent repetition of the dosage, and from its quicker elimination unchanged from the body, its chance of forming a habit is very small indeed. One patient under the writer's care had to take his codeine at least once every hour when awake. In ratio to the amount used in therapeutics, the chance of habit formation is practically negligible. In this regard it should not be classified as a narcotic. It should be classified and considered as one of the most useful of the analgesics.

HEROIN ADDICTION

Heroin on the other hand, is one of the most evil and dangerous of drugs. Heroin does not occur in crude opium, it is a synthetic preparation, made from two molecules of morphine, it is diacetyl morphine. Heroin was first used in this country in about 1909, and it soon became evident that it possessed all the habit-forming properties, even stronger than morphine. Its intense narcotization of the emotional centres of the brain, destroying the sense of emotional values, is extraordinary, and more rapid than morphine. It benumbs pain, and it is said that in patients dying of malignant disease, it quiets unbearable pains with less stupefaction of the mentality than morphine produces. It is highly recommended to allay cough, but in pneumonia it is not without danger, as a respiratory paralyzer when given to allay the distressing cough of this malady.

In the cities of the eastern United States the heroin habit has grown to alarming proportions, and most of the younger addicts of thirty years of age or less are heroin takers. Heroin appeals to the young, because it inflates the personality, and gives a sense of stimulation which morphine does only in its early stages. In the narcotic clinic of the New York Health Department, it was noticeable that those who were addicted to heroin, and they formed the vast majority of the addicts who came to that clinic, were not the thin emaciated and starved type of individual seen among the former chronic takers of morphine of former days, but many of them appeared apparently normal physically, Many of these were of constitutionally inferior type, and many were of the underworld. Many of these believed they never had had a square deal, and their environment had been such as to convince them of this. What their mental convictions were, or had been, was not definitely studied, but it was very evident that heroin answered and solved the problems of an unhappy life. These usually were those of hurt personality, of a feeling of resentment for the lack of better opportunities. They were convinced that they were misunderstood, and they often were out of harmony with their environment, and the mental struggle of reorganization to their environment was more than they could bear. When something, therefore, was offered to them which inflated their personality and enabled them to inagine that they were a more successful and ideal being, or that they were some hero of their choice, the substance was eagerly seized, and soon became a dominating necessity to them. With the habit formed, all

sense of responsibility becomes annihilated, and they become antisocial. Heroin was often begun to stimulate after dissipation, to enable them to do their daily work. These heroin addicts will commit any crime to obtain their drug, and for any reason whatever that seems to them sufficient. They are antisocial savages, without any restraining influence except that of their own selfish interest, and restrained only by fear of punishment, or by lack of opportunity to commit a crime.

These patients lack all feeling of necessity to put up a defence reaction, but will deliberately formulate a lie without hesitation to obtain anything they wish. Stealing and prostitution is done without hesitation, with a full realization of what they are doing, and with cold-blooded indifference. There is no moral restraint, and no remorse.

Heroin addiction is a public menace, as it increases the rebellious attitude of antisocial youth, and obliterates all controlling influences of the herd instinct. Heroin, under these circumstances, is naturally the drug of choice of the criminal class. It gives them the desired inflation of personality, the reckless daring, the indifference to crime, and the lack of all remorse, no matter what crime is committed. Its good effects can be obtained by other salts of opium, its evil effects are its own, not shared by the other opiates.

Heroin is taken by snuffing in the nose, or by mouth, or by hypodermic injections. The amount of heroin taken may run up from 30 to 60 gr. a day, 60 gr. a day being an extremely high dosage.

If cocaine be added to heroin the degeneration of the personality is more rapid and intense than with either taken singly. It is easier for patients to cut themselves off from heroin, than from morphine, for the suffering is not so drawn out, nor is there the intensity of cardiac and vascular collapse produced by the withdrawal of morphine. The vomiting and purging are not present, nor is the intense nervous trembling from which the chronic morphine patient suffers. The withdrawal symptoms seem of shorter duration, and the pains do not persist as long as in the chronic morphinist.

MORPHINISM

Indulgence in morphine is a development of recent years; it has taken the place, especially in large cities, of the preparations of crude opium. The readiness and cheapness with which morphine can be obtained and the ease with which hypodermic syringes can be bought have made this addiction a widespread curse.

The taking of opium or its alkaloids produces no pathological lesion which can be demonstrated by postmortem examination. Even after years of morphine taking, the patient can recover from the poisoning and return to vigorous health in bodily function, and to the unconscious exhibition of his normal personality. This cannot be done after severe and prolonged poisoning by alcohol, which produces definite demonstrable lesions in the body. This indicates clearly that the addiction to any opiate produces only a functional poisoning of the tissues, and does not produce a disease in the ordinary acceptation of the term. The claim of Marme, Valenti, Bishop and others that morphine addiction is a disease

because there is an antibody or a toxin formed during morphine habituation, has been disproved by Pellini and Greenfield, who have proved that there is no antitoxin formed in the tolerance gained by morphine habituation, nor is there a toxic substance formed by this same habituation, which can be proved as circulating in the blood. The rapidity with which animals and man lose their acquired tolerance for morphine points to a functional balance or change, rather than a tissue lesion. Many patients have suffered from acute morphine poisoning and death shortly after their habituation was broken off, when on returning to their drug they took their former accustomed dose, believing such dosage necessary to obtain the desired effect. Scott Loria and Tardo have recently shown that morphine injected into the portal circulation can be recovered from the general circulation after its passage through the liver, but it has become so altered that it is innocuous and produces no symptoms of morphine poisoning when injected into susceptible animals. This substance gives the reaction of pseudomorphine, or oxydimorphine, described by Faust, Cloetta and Marme as the substance into which the animal body converts morphine. It seems therefore that the liver plays an important role in the destruction of morphine in the body, and it may well be that an increased ability of the liver to change morphine to an innocuous substance may be a large factor in morphine tolerance. The exact mechanism of morphine tolerance is still unknown.

Morphine addiction is a chronic functional poisoning of the mid-brain centres, and the vegetative nervous system, which are the centres of conscious sensations and emotional values, and the nerves of functional and trophic equilibrium of the unconscious physiological functions of the body. Man takes morphine when the physical sensation of pain becomes unbearable, or when the emotions of sorrow, disappointment, and unhappiness are so intense they cannot be suffered without relief. Morphine is taken to benumb and keep benumbed these centres, and such a functional poisoning does not constitute a disease, for full functional recovery rapidly occurs as soon as morphine is properly cleaned out.

The withdrawal symptoms of morphine are the expression of the disorderly disequilibrium between the parasympathetic and sympathetic portions of the vegetative nervous system controlling the functions of the digestive, circulatory and glandular systems of the body with the return of the sensation of pain in consciousness.

The question may arise in the case of a patient suffering from a painful and incurable disease, whether a physician is justified in giving morphine, knowing that if once used it must be given for the remainder of the patient's life. True it is that morphine given daily for two or three weeks, even in small doses, is sufficient to cause a habit, although many patients resist longer than this. The habit is always formed through the repeated administration of small doses, and the idea that because the dose is small no habit will follow has led to many addictions. Although people are often opposed to having it said that members of their family died with the morphine habit, yet in many cases of incurable disease it is simply cruelty to refuse to give it and the formation of a habit in some sufferers is of no consequence.

The hypodermic use of morphine is the most seductive form of the habit and the hardest to break; some patients seem to require the sensation of the needle thrust in order to be satisfied. In many who take enormous doses it would seem that all the morphine does not act, but some must remain inert and be excreted without action. Mithridatism, or the inability to be killed by opium and morphine, seems to occur in those taking over 30 gr. a day. The writer has seen one patient take in a single dose 45 gr. of morphine hypodermically and only become comfortably drowsy, and another patient take 47 gr. within two hours, and show no effect except satisfied contentment.

Considering the symptoms, memory is one of the faculties first affected and the amnesia is similar to the beginning senile dementia. Names are the first to go; the morphinist will relate occurrences early in his life, but will forget what he has done during the past week. He will forget the familiar names of streets, the details of his profession; thus the physician forgets the dosage of medicines and the scientific terms with which he is familiar. Amnesia of the well-marked stage of morphine intoxication is only equalled by the amnesia of paresis. The will power is enfeebled and the patients spend days in bed without sleeping and without stupor; their minds are perfectly clear but their power to do is gone. In some patients this is continuous and permanent; in others it seems to run in crises, lasting over two or three days. There is psychic asthenia. The sense of responsibility is wiped out and is replaced by the indifference of perfect egotism. Their character is modified and they are discontented grumblers, obstinately "ugly," often given to explosions of intense rage, quarrelling without cause, and even destructive and dangerous to those with whom they come in contact. Often the morphinists are individuals of more than average ability and intelligence, realizing fully their condition, and appreciating their progressive degeneration. It is for this reason that they resent criticism and accept reproaches about their habit with bad grace, because they are already filled with remorse. Morphinists usually lie about their addiction because in the early stages they feel that others consider it a vice and a disgrace, however innocently it may have been acquired, and they have enough moral sense left to endeavor to hide it. If, however, they have just taken their morphine or are assured of sufficient dosage to keep them comfortable, they do not necessarily lie about other matters. The fear of being deprived of their drug is an ever-present horror. Patients have come under the writer's notice who were literally starving to death and yet they had money kept to procure the necessary amount of morphine to prevent them going through the horrors of forced withdrawal without assistance. When the craving for the drug is upon them there is nothing to which they will not stoop to obtain it. Lying, thieving, begging in the street, prostitution itself, are to them all justifiable means to obtain the drug.

Morphinists do not sleep well; they are subject to nocturnal hallucinations which render their nights times of terror; thus they endeavor to keep themselves awake by reading, and during the daytime are prone to fall asleep whenever they remain quiet, sitting in a chair, no matter

in what place or company. The hallucinations of sight are always terrifying, and contrary to the hallucinations of alcoholism, those of morphinism are not occupation deliriums. The hallucinations of sight are the most frequent; next those of hearing; those of taste and smell are rare, and those of general sensibility are exceptional, which last is also contrary to what occurs in alcoholism. The sense of taste is often dulled and sometimes even abolished. Reading and writing become impossible because objects appear clouded and deformed, and when the endeavor is made to fix an object, it dances or trembles or approaches or retrogrades, and this, together with a frequent distinct photophobia, causes great distress. Ophthalmoscopic examination does not reveal any distinct lesion. There is at times contraction, and at times dilatation, of the pupils; an anemia of the retina has been described. The visual disturbances disappear when the morphine is permanently withdrawn. The reflexes are very variable. Disturbances of the general sensibility are often marked and vary greatly; there are often paresthesias and sometimes intense neuralgic pains. Others show marked anesthesia, which may be confined to one side of the body. More often there is hyperesthesia, and the sole of the foot becomes so painful, that, when it is touched to the floor, it gives a sensation of burning, and the patient can only walk with short, jumping steps. Rodet considers this form of hyperesthesia as very characteristic of chronic morphinism. The tactile sensibility is usually diminished or abolished. The question often arises whether indulgence in morphine impels the individual to suicide. At times when, inadvertently, too large a dose is taken, the patient succumbs, but as long as he can obtain his drug, he is an individual without will, apathetic, and incapable of making exertion to commit suicide; if, however, the morphine be withdrawn or he cannot obtain it, the situation entirely changes.

Troubles of digestion are common; in the early stages there is nausea, vomiting, and anorexia, which do not persist for a very long time. There is often an intense thirst; the breath is very offensive and of a peculiar odor, often spoken of as being so characteristic as to designate the morphinist by those who are brought in contact with many of these patients. Constipation is marked and often alternates with attacks of diarrhœa; the stools are sometimes bloody and, during the period of constipation, may be as infrequent as once or twice a month. The teeth are subject to caries, which attacks first the molars on their grinding surfaces; this extends to the bicuspids, then to the incisors, and last of all to the canines. This is always painless, not accompanied by any periostitis, and usually progresses with great rapidity. It usually coincides with the falling out of the hair. The disturbances of nutrition appear in some patients after a few months and in others not until after some years. Emaciation is perhaps the most striking and may go on to an extreme degree. Their faces becomes livid and often sallow, the expression set, and there are premature wrinkles, which, with the faded, sallow look of the skin, often gives the look of premature old age. The tissues lose their vitality, which accounts in a measure for the ease with which slight bruises cause ecchymosis, and the greater liability to the occurrence of abscesses. Many

persons taking relatively small doses of morphine, from 1 to 5 grains a day, may not show any evidences of their habit for years, except the small pupils and slight pallor. Only to those in intimate contact will any change in mentality or disposition be evident, and even then the cause is often unsuspected.

The pulse of the chronic morphinist is slow and there is a fall in arterial tension with, in the last stages, distinct enfeeblement of the heart's action and diminution in the force. The number of respirations is slowed and, at times, they are shorter, so that every now and then a long deep inspiration seems necessary to give the required amount of air. Dyspnœa on exertion, even of the slightest kind, is quite common. In the beginning of morphine addiction there is polyuria, which later is followed by a diminution of secretion below the normal. In many there is albuminuria which is ascribed by Levinstein to a special action of morphine on the medulla, to changes in the arterial pressure, or to a paralysis of the nerves which enter the kidney around the renal artery. The effects in the genito-urinary system are much the same as those described under opium.

Most women become sterile, but in spite of the cessation of menstruation, conception may take place. Pregnancy may run its normal course, or the morphine may cause a miscarriage or premature birth. Children born of morphinist mothers may be well-formed and normally healthy. Often the children of morphinist parents are idiotic or show a lack of mental and physical development.

The accidents which may follow the injection of morphine are those of infection from the use of a dirty needle or of an infected solution. These abscesses usually appear at the point of injection, but sometimes at distant points, in a portion of the skin which has not been perforated. They are usually small, rather indolent, and not always as painful as one would expect. They usually heal under proper treatment, although they may form indolent ulcers. The points of injection may be the starting point of erysipelas, cellulitis, or phlegmon. Kane reports cases of tetanus developing from the hypodermic injection of morphine. Where the morphine has been injected directly into a vein, sometimes a sudden, intense narcotism follows and the patient feels a peculiar tingling over the entire body. This is followed by a feeling of great fulness and throbbing in the head, and may be accompanied by difficulty of respiration, swelling of the face, and loss of consciousness. Death has been reported as following quickly when morphine is suddenly injected into the circulation. Most habitués increase the dose so gradually that the accident of acute poisoning and death from an overdose is comparatively rare. When, however, an endeavor has been made to reduce the amount taken and then for some reason a larger dose is desired, an amount, which formerly could be borne with impunity, is taken and death results.

When once a person is thoroughly under the influence of the habit, a cessation of the use of the drug produces symptoms, both physical and mental, of such intensity that few are strong enough to resist the craving thus produced and, unaided, break off the habit. When the effects of the last injection begin to wear off, restlessness, malaise, yawning, and sneezing appear; the craving increases and can only be entirely

relieved by a further dose. The length of time, after the last dose, at which these symptoms will begin, depends on the individual. Following quickly on the malaise, the eyes begin to water and the eyelids droop. The eyes lose their lustre and vision is much disturbed. The face becomes pale and an expression of intense distress is very noticeable. There is a trembling of the hands and of the arm, varying markedly from the alcoholic tremor. In this condition there is nothing that morphinists will not do to obtain the drug. As enforced abstinence continues, the patient may develop epileptiform attacks or hysteria, or there may be in neurotic individuals a state of choreic jactitation. In extreme cases a form of mania may develop in which the patient endeavors to commit suicide or attacks the attendants. Hallucinations of sight and hearing may develop, and these are always of a terrifying nature. This is most frequently seen in those who have taken cocaine or alcohol with their morphine, but not infrequently in those who have taken morphine alone. Often, before these mental disturbances are fully developed, the patients are overcome with a sensation of extreme weakness and forced to keep in bed. They are pale and haggard; there is nausea and vomiting, and almost invariably diarrhœa, which may be profuse. This is often accompanied by intense abdominal pain and hyperesthesia of the skin, so that the patient can scarcely support the weight of the bedclothes; the body is often covered with a cold sweat, and there may be chills of great intensity.

When morphine is cut off abruptly there is great danger of collapse. This may supervene on the second or third day, and the patient shows increased weakness, appears pinched and haggard, while the pulse becomes small and then disappears. Or he may show a sudden high-pulse tension, feebleness of the heart action, and suddenly, while wandering about restlessly, fall pulseless to the floor. Sometimes the fatal collapse may occur without warning while the patient is quiet. Still another form of collapse may occur; the face becomes deep red, the eyes shine brilliantly, the pulse falls to 40 and the patient loses consciousness after a feeling of intense agony. These collapses may last for fifteen or twenty minutes; they may recur three or four times in the twenty-four hours, and the patient may recover or die in any of them unless morphine be given. Fortunately these attacks are rare when the drug is withdrawn gradually but they are fairly common when this is done abruptly. There are some few cases on record in which the fatal collapse occurred some time after the patient was convalescent and apparently well on the road to recovery. During their periods of suffering, the patients are apt to be afflicted with distressing insomnia, and, if they sleep, it is only in fitful dozes. In a longer or shorter time the suffering gradually subsides and the patient can rest with some degree of comfort; the morbid craving has gone; the appetite returns and often becomes excessive; in women menstruation is reëstablished, at first painfully, later normally. In both sexes the sexual desire returns, often painfully and excessively and then subsides. The patient goes into a rapid convalescence. When morphine is broken off, if it has been taken to quiet some neuralgia or to benumb some unbearable sensation, these pains, although quiescent during the period of the addiction, may return in full force as the morphine is removed.

Treatment.—Most patients addicted to morphine have long ceased to obtain any pleasure from its use. They long to be free from its slavery and dread only the terrible suffering which the deprivation from the drug brings. The question arises whether they should be treated by the slow withdrawal method, in which they are treated symptomatically for whatever symptom seems most distressing, or whether the drug should be withdrawn abruptly and the patients suffer with full intensity, hoping to relieve them in a shorter space of time, or whether some of the more recent methods, using belladonna or hyoscine, should be employed.

The sudden withdrawal method does not seem justifiable. The danger of sudden collapse and death is not a theoretical one. Morphinism or the opium habit is a chronic poisoning and must be treated as such. The most effective method is by the rapid elimination of the drug in the body, the quieting of the withdrawal symptoms with some preparation of the belladonna group, and as rapid a withdrawal of the drug as the condition of the patient will justify. Under these conditions collapse need not be feared, and the elimination of the poison and the restitution to health is soonest accomplished.

Lott, of Texas, was the first to use hyoscine in the treatment of morphinism, giving gr. $\frac{1}{100}$ of the hydrobromide hypodermically every two hours for two or more days during which the morphine was withdrawn. The patient does not sleep but lies stupefied, mumbling continuously and picking in a restless delirium Petty modified the hyoscine treatment, and used it successfully to break off opiate addictions.

Braunlich's method in the New York City Health Department is as follows: Patients are admitted to the hospital through an examination room where they are undressed; they are then taken to a second room for a thorough cleansing and then to a third room where hospital clothing is provided, this being necessary to rid them of drugs that they may have brought hidden with them. They are then switched from heroin to morphine, and if accustomed to a large daily dose of this, they are given 5 or 6 gr. in the first twenty-four hours; at the end of the fifth day the daily quantity has been reduced to from $1\frac{1}{2}$ to 3 gr. of morphine, elimination having been caused during this reduction period, by the use of cathartics given on the fourth and sixth days. The cathartic used in this treatment is $2\frac{1}{2}$ gr. of calomel, $2\frac{1}{2}$ gr. powdered rhubarb; $\frac{1}{2}$ gr. powdered ipecac, $\frac{1}{100}$ gr. atropine sulphate and $\frac{1}{30}$ gr. strychnine sulphate; it is given, at 3, 6 and 9 P.M. On the seventh day a large dose of castor oil is given, and the last dose of morphine, amounting to $\frac{1}{2}$ gr. The patient is then put in the hyoscine wards, and when he becomes uncomfortable from the wearing off of the effects of the last dose of morphine, he is given $\frac{1}{200}$ gr. of hyoscine hypodermically, repeated at intervals frequent enough to keep up an anesthesia corresponding to the first stage of ether narcosis, characterized by a mild delirium, occasional jerky muscular movements, and usually a reduction in the pulse-rate. This anesthesia is kept up for thirty-six hours. If the patient becomes very agitated—sometimes he may become maniacal—a dose of $\frac{1}{4}$ gr. of morphine is given without hesitation; this is quieting and does not in any way lengthen the duration

of the treatment. The amount of hyoscine given in the first thirty-six hours carries the patient over the last thirty-six, as withdrawal symptoms do not extend over seventy-two hours. If, after this length of time, the patient is suffering too intensely or vomiting too severely, he is given a few more doses of hyoscine by mouth or hypodermically. About the tenth day after admission, he is placed in the convalescent ward and although much weakened, he is more or less up and around. Because of sleeplessness and muscular weakness, he is at his worst as far as craving for this narcotic is concerned, and it is during this period of the treatment that he needs the most careful watching. He craves the drug, and if he can get it he will use it. He is given bromide and chloral. If the pulse is weak he is given spartein sulphate and strychnine, occasionally combined with $\frac{1}{10}$ gr. apomorphine. These three together make a very soothing dose. After a week in the convalescent ward, the patient is sent to a dormitory and given occupation and receives no further medication except for intercurrent diseases. Regular diet is given up to the time of entering the hyoscine wards, nothing but water in the hyoscine wards, and after that, regular diet again as soon as it can be taken.

After an extended experience of the hyoscine treatment, and the resulting effect on the patient, Braunlich takes a very pessimistic view of the possibilities of eradicating the desire for the drug from the minds of the patients addicted to it. He believes that the only chance lies in preventing patients from obtaining it. "The memories stored up in the brain of what the drug will do for him in the way of relieving worries, pain and exhaustion are fixed, and it is doubtful if they ever disappear. In other words, under certain conditions, a man who has once been an habitué is in danger of relapse even though he has not had morphine for years." Braunlich however, admits, that "proper treatment covering a protracted length of time will result in more cures than slip-shod, stereotyped methods."

Stokes' method, useful where small doses of the narcotic are taken, is by the administration of eserine and pilocarpine. This seems particularly useful in heroin cases. It has not been found satisfactory by the writer in patients who have taken morphine for several years, but in those who have been taking small doses of morphine for a short time, and in patients taking small amounts of heroin, it has proved very useful, The patient receives preliminary catharsis and an initial dose of about $\frac{1}{2}$ gr. of heroin or morphine, and is given hypodermically $\frac{1}{50}$ gr. of eserine and $\frac{1}{15}$ gr. of pilocarpine. This will keep him comfortable for a short time, but not longer than three hours, and the eserine and pilocarpine may be repeated at intervals of two and a half hours. After twenty-four hours the eserine should be discontinued, but the pilocarpine should be kept up for two or three days longer, the interval between doses being lengthened toward the end of the treatment. The patient should have sufficient cathartic each night to produce a good result the following day. If, during the treatment, the patient shows too much restlessness and withdrawal symptoms, he can be quieted with a small dose of morphine from time to time. Some young patients who have been taking heroin develop an enormous appetite under this treatment, but they should not be allowed to overeat.

Comparing the effect of these treatments on the desire or craving for the opiate; hyoscine does not obliterate it, the patient gradually loses his desire as he slowly recovers from the utter weakness left by the hyoscine. The belladonna treatment does obliterate the craving, by the time the treatment is finished, in spite of the weakness felt. In a few days the patients are cheerful and active.

Another treatment is known as the Towns method. This has the advantage that the belladonna and hyoscyamus do not bring the patients to a stage of delirium nor to the condition of helpless unconsciousness as hyoscine does. These drugs are never pushed beyond the stage of dry throat and dilated pupils; the patients retain their consciousness and freedom of action. The mixture consists of 2 parts of a 15 per cent. tincture of belladonna and 1 part each of fluidextract of hyoscyamus and xanthoxylum. The best results are obtained when this mixture is pushed to the patient's tolerance for belladonna. This varies and some of the best results have been obtained with patients who could not tolerate more than 2 drops of this mixture as an hourly dose, while in others it was necessary to push the mixture up to 18 or 20 drops or even more. The bottle containing the mixture must be kept well corked and shaken before using. The details of the method are as follows:

The patient is given 3 to 5 compound cathartic pills and 5 gr. of blue mass, and six hours later, if these have not acted, they are followed by a saline; after three or four abundant movements of the bowels the patient is given, in three divided doses at half-hour intervals, two-thirds or three-fourths of the total daily twenty-four-hour dose of morphine or opium to which he has been accustomed. The larger amount of the drug is an advantage as the patient is less likely to feel discomfort just before his next dose. If patients are taking 5 gr. or less of morphine a day, they usually can stand the full amount of morphine they are taking in each twenty-four hours as the initial dose, divided of course in three doses at half-hour intervals. Most patients are ashamed to tell the amount of drug they are taking. Take therefore the highest amount spoken of as the daily dose as being the usual daily dose. Observe carefully, however, after the second dose has been given, as the amount then equals four-ninths or one-half the total twenty-four-hour dose. Some patients cannot comfortably take more than this amount. With the last dose of morphine, the 6 drops of the belladonna mixture are given in capsule. This belladonna mixture in doses of 6 drops (from an ordinary medicine dropper—not minims) is given every hour for six hours. At the end of six hours the dosage is increased 2 drops. The belladonna mixture is continued every hour day and night continuously throughout the treatment, increasing 2 drops every six hours until 16 drops are taken, when it is continued at this dosage; it is diminished or discontinued at any time if the patient shows belladonna symptoms, such as dilated pupils, dry throat, or redness of the skin, or the peculiar incisive and insistent voice, and insistence on one or two ideas. It is begun again at reduced dosage after the above symptoms have subsided, that is, after three or four hours begin again with half the former dosage and at six hour intervals increase by 2 drops.

At the tenth hour after the initial dose of morphine is given, the

patient is again given 3 to 5 compound cathartic pills and 5 gr. of blue mass. These should act in six or eight hours, but if not a vigorous saline is given; when they have acted thoroughly, the second dose of morphine is given, which is usually about the eighteenth hour. This should be one-half the original dose, *i. e.*, one-third or three-eighths of the original twenty-four-hour daily dose. The belladonna mixture is still continued, and ten hours after the second dose of morphine, that is about the twenty-eighth hour, 3 to 5 compound cathartic pills are again given and 5 gr. of blue mass; these if necessary followed by a saline six or seven hours later. After these have thoroughly acted at about the thirty-sixth hour, the third dose of morphine is given, which is one-sixth or three-sixteenths of the original dose. This is usually the last dose of morphine that is necessary. Again, ten hours after this third dose of morphine, *i. e.*, the forty-sixth hour, 3 to 5 compound cathartic pills and 5 gr. of blue mass are again given, followed seven or eight hours afterward by a saline, and one expects at this time to see a green stool appear. When this appears, after the bowels have moved thoroughly, about eighteen hours after the third dose of morphine, 2 ounces of castor oil are given. If at any time a patient is nauseated, calomel in small doses with a little soda can be given at half-hour intervals instead of the cathartic pills. Sometimes about the thirty-sixth hour of treatment the stools will become clay-colored. Small doses of ox-gall given for a few hours at hourly intervals will further stimulate biliary secretion. Often it is necessary to give a fourth dose of morphine, one-half the third dose and to continue the belladonna mixture for one or two further cathartic periods before the bilious stool will appear, codeine being used to ease discomfort. The discomfort from the morphine withdrawal usually begins between the second and third dose of morphine. Codeine should be begun then and given with 30 to 60 ♏ of a 0.125 per cent. sterile solution of magnesium sulphate hypodermically. These can be given at four to six-hour intervals and quiet the muscular restlessness, pains and twitchings better than hypnotics. Often the magnesium can be repeated without the codeine. At first 5 gr. of codeine can be given, but later in the treatment this can be reduced to 3, 2 or 1 gr. Enough codeine must be given to relieve suffering. When given between the second, third or fourth doses of morphine, the actual amount of codeine given is of no serious consequence. A firm endeavor to diminish the codeine must be made so that when the castor oil is given the further use of codeine will not be necessary. Codeine continued subsequently is treacherous and continues the narcotic craving. The use of the magnesium diminishes the necessity for the codeine. Chloral or bromides can be given to relieve the abdominal pains which some of the patients suffer as part of their withdrawal pains, and which are not due to the vigorous catharsis. Ten grains of chloral and 15 gr. of bromide every four, six or eight hours, reduces the restlessness and quiets the apprehension and diminishes the abdominal reflexes. Sodium bromide continued for twenty-four to forty-eight hours after cessation of treatment in diminished doses, relieves the sleeplessness from which these patients suffer. Pain in these patients can often be relieved by some combination between phenacetin, antipyrin or pyra-

midon, and aspirin or sodium salicylate with sodium bicarbonate and caffeine. About the thirtieth hour these patients should be given strychnine or digitalis, or both. After they are free of morphine, the tonics which do the most good are those which contain some form of phosphorus and arsenic.

There is a danger during convalescence in overeating, and thus bringing back withdrawal symptoms due to disturbance of digestion. They have been in the habit of referring all uncomfortable feelings to the withdrawal of morphine, and digestive disturbances feign these symptoms.

The question arises whether the treatment should be undertaken in the patient's home or in some institution. There is no question, if patients will go to an institution, that they will go through with less pain and suffering, for they will be cared for by physicians who are dealing with this treatment and alleviating the symptoms which vary in each individual patient; and a morphine patient requires constant attention.

Sometimes it is wise to carry on the morphine through the fourth period, not cutting it off after the third, especially in those who are taking large doses and who are physically much below par. When giving codeine for the relief of nervousness and distress, it is safe to calculate that 1 gr. of codeine is equal to $\frac{1}{8}$ gr. of morphine, and $\frac{1}{2}$ gr. of dionin is equal to about 1 gr. of codeine. Heroin, is dangerous to give in tiding over the distress, simply because it is adding to the narcotic, and codeine and dionin are preferable. But if a patient is given codeine or dionin longer than forty-eight hours after morphine is stopped he will acquire the necessity for codeine or dionin. Patients sometimes show an idiosyncrasy against codeine and it produces a burning and redness of the skin or sometimes an urticarial rash with intense heat and itching. This quickly passes, but dionin will have to be substituted. The ambulatory treatment in which the patient is given his drug and told to reduce it as best he can, has been tried by several generations of physicians, and with almost universal failure. Few indeed are the human beings, who unaided, can break themselves of the narcotic habit.

The after treatment is of great importance. The patient should be built up physically. Men should be sent to some physical trainer where they are built up into good physical condition. If this is not done they drift into an irritable, discouraged, neurasthenic condition in which they are very prone to go back to their narcotic. If, however, they are properly built up, at the end of a month they will have gained flesh, their anemia will have disappeared, and they will be in excellent health and spirits. Morphine or opium in any form must be strictly guarded against. These patients must have their psychology reorganized to rid them of their unhappy memories and problems, or so rearranged as to be able to face their problems and face the realities of life. Their environment must often be changed.

COCAINE

The pure cocaine habitué is not as common as the morphinist or the alcoholic. The drug is usually taken to overcome the nervousness of an alcoholic debauch or the depression following morphine. It is not

infrequently used to relieve the exhaustion following sexual and alcoholic excesses. Judging from the statistics of drug-store sales, cocaine habitués seem to be most common among the very poor and among the wealthy. Cocaine is contained in certain quack nostrums. In the Southern States, cocaine addiction is very common among the negroes. Snuffing the powder or a solution of cocaine is a common method of use. It is often taken hypodermically, and, when thus used in impure form, it sometimes causes a green discoloration, which remains permanent at the site of the injection in the skin. Patients suffering from neuralgia, local or general, physicians exhausted and anemic, who have to be tided over some strain, neurotic and psychopathic individuals, the wornout and failures of modern life, fall easy victims.

Acute cocaine poisoning is seen following the injection of the drug to obtain its local effect in surgery. Death is reported as having occurred in forty seconds following 12 drops of a 4 per cent. solution given hypodermically to a girl aged eleven years. Half a grain to one unaccustomed to its use seems often to be a borderline dose. Such small doses as 4 drops of a 2 per cent. solution in the eye, produced in an old woman an intoxication which lasted for four days, and even 1 drop of a 1 per cent. solution in the eye of a child, aged fourteen years, has been followed by symptoms of active poisoning. There is a strong idiosyncrasy, and while such small doses have caused death, recovery has followed such large doses as 22 gr. by the mouth and 10 gr. hypodermically. In the mild cases of poisoning the ordinary symptoms are great restlessness and nervous excitement, with no feelings of pleasure or comfort, but rather those of anxiety and even terror, an increase in the frequency of the respirations, and often a distinctly accelerated pulse-rate, with the patient pale, faint, and dizzy. In the more severe poisoning there are severe nausea and vomiting, a rapid and imperceptible pulse, great nervousness and jactitation; the patient feels as if the heart would stop beating; intense perspiration and collapse with or without loss of consciousness are seen; the pupils are usually dilated; in some they have been reported as contracted, and, occasionally, the pulse has been slow and feeble with slow and infrequent respiration, or Cheyne-Stokes breathing with marked cyanosis. After large doses, convulsions are frequent and often of a violent epileptiform character. At times these are partial, with unilateral or bilateral cramps in the muscles, chiefly in the flexors; these muscular spasms may go on to general rigidity and opisthotonos may be produced. Consciousness is usually lost but sometimes there is mania with hallucinations and delusions which have frequently been violent and even homicidal.

The *treatment* of the poisoning is symptomatic: the patient should be kept in a horizontal position and given aromatic spirit of ammonia, alcohol camphor, or caffeine. If the poisonous effects are manifested in the respiration, oxygen or even artificial respiration should be used. Intravenous injections of normal saline solution have proved helpful. If the drug has been taken by the mouth, the stomach should be washed out. After the patients have recovered from this acute poisoning, nervous disturbances, such as insomnia, vertigo, tingling in the limbs, and mental depression, may continue for some days.

Chronic poisoning by cocaine is both periodic and continuous. The periodic form is characterized by the excessive use of the drug for several days or weeks, after which it is abandoned and there is a period during which there is no desire for it. During the free intervals the patient remembers distinctly the pleasurable impression which he obtained and declares that he has broken from its use and that he will not use it again, but as soon as the cause returns which formerly drove him to the use of the drug, he will invariably reason that there is no danger in using it for a short time, and resumes its use. Soon the free periods become shorter, and those of addiction longer, and its use becomes continuous. These persons also show the peculiarity that in order to conceal the habit they take other drugs, such as alcohol, chloral, and morphine, and when they cannot obtain cocaine they turn to any drug that will quiet the nervous system. Some become violently maniacal, but when given cocaine almost instantly quiet down.

The main pleasurable action is the feeling of exhilaration and increased mental and muscular strength and with this there soon develop delusions of great strength and vigor, the patient feeling as if he had absolute self-possession; he shows great activity, talks freely, and enjoys everything; each sense seems to be gently heightened. Finally hallucinations of voices begin to appear; there are delusions of persecution and fears of personal injury; insomnia comes on with great muscular restlessness and agitation, which simulates the irregular spasmodic movements of chorea major. They show a profuse volubility, talking in a wide discursive manner over all subjects and in their writing or speech there are no pauses, no dividing lines, no purposeful connection but a steady, connected flow of words, involved and without point, without direction, and without end. The patient will endeavor to convey some idea or belief, and after the first few sentences the purpose is forgotten and he wanders on in great prolixity and diffuseness. Thus many cocainists are great letter-writers, and in some instances the letters have taken on an amatory type. This same prolix type, in other instances, has taken on a slanderous form, but there is a noticeable lack of bitter, sharp accusations and distinct charges; the meaning of the letters can only be made out by inference from the involved mass of words. Again, hallucinations of sight and hearing develop, and the patients see suspicious characters watching them and hear voices plotting to do them injury; they begin to take unusual precautions and are prone to carry revolvers and knives to defend themselves.

In the early stages of cocainism, when the effect of the drug begins to wear off, the patients become morose, irritable, easily excited, and suspicious; there is insomnia and an impending sense of trouble and danger. In the later stages, the exaltation periods are brief and are followed by stupor and restlessness with evidences of great mental disturbance. The appetite fails; they are anemic, and emaciate very rapidly; look sleepy and tired; the skin becomes flaccid and pale; the senses of sight, hearing, and smell are seriously impaired, and there is a feeling of paresthesia in the skin, giving a sensation as if vermin were crawling on it, which is a very significant symptom. Although there is increased sexual

excitement, the sexual power is diminished. Kraepelin describes a definite psychosis which may develop on the basis of chronic cocainism and which bears a close resemblance to alcoholic delusional insanity. It begins with a few days of irritability, anxiety, and restlessness, after which the hallucinations suddenly appear. Threatening voices are heard compelling the patients to act strangely; moving pictures are seen on the wall. Minute black specks, moving on a light surface, are very characteristic hallucinations, and may be mistaken for flies, mosquitoes, and other small objects. Paresthesias of the skin create the belief that they are under the influence of electricity or are being punctured with needles. Most characteristic is the sensation of foreign bodies under the skin, particularly of the ends of the fingers and palms of the hands. Auditory hallucinations make them suspicious of their surroundings. They believe their thoughts are secretly being read or they are being spied upon through holes in the ceiling. The patients may try to kill their alleged tormentors or attempt suicide. They have characteristic delusions of infidelity which come on as an acute symptom. These are often obscene in character and they will accuse their wives of the grossest immorality. They are prone to react to these false ideas in a vindictive and aggressive manner. Consciousness remains clear and orientation is good except in rare instances when the excitement is very great or after the fresh injection of the drug. The emotional attitude is dejected, excitable, irritable, and even passionate; more rarely they are reserved and reticent concerning their delusions. Their actions are usually restless and unstable, though some may appear orderly.

Cocaine delusional insanity develops rapidly and may run its full course in a few weeks. The symptoms increase under the influence of a single dose. The delirious state soon disappears if the drug be completely withdrawn, but the delusions may remain for weeks or months. Morphinism and cocainism in the same individual often lead to a combination of symptoms, but morphinism, except with cocainism, seldom produces a rapid development of pronounced mental disturbance. The cocaine psychosis develops more rapidly, the symptoms are more severe than in the alcoholic delusional insanity, and the delusions of jealousy appear earlier and are an acute symptom. A single dose of cocaine produces an exacerbation of the symptoms, while in alcoholism it produces little or no effect. The sensation of objects under the skin is characteristic only of cocainism.

Diagnosis.—This is often very difficult. In some patients there is only an increased buoyancy of spirits and an increased desire for mental and physical exertion, but if their work is studied closely, its character and the judgment displayed in doing it are below the former excellence. These patients show defects of judgment and a diminished sense of ethical duties; they are also more prone to be reckless and aimless in their thoughts and work, and show a diminution of ambition and will power. The powers of connected application are less, and often a noticeable symptom is periods of buoyancy varying with periods of beginning depression, and a disposition on the part of the patient to go off alone; and on his return the old buoyancy and confidence have returned. Thus

the cocainist differs from the alcoholic by his periods of secretive solitude and from the morphinist, in the later stages, by his delusions of persecution. When cocaine is the main drug and alcohol and morphine are taken to relieve it, the periods of exaltation and delusions of persecution are very noticeable. If cocaine is taken to relieve morphine or alcohol, the peculiar symptoms of cocaine are usually absent and there is simply a restlessness and insomnia. Morphine and alcohol, taken after cocaine, intensify the injury to the nervous system and both mania and dementia are apt to follow.

Prognosis.—In the early stages, when cocaine is taken alone, if the proper treatment can be instituted, the habit seems to be more easily broken than that of morphine or alcohol and the chances of a permanent cure are greater. If, however, the habit is well-established, complete recovery is obtained with greater difficulty.

Treatment.—In treating cocainism we must realize that there is no drug which brings with it such a blissful sense of satisfaction and of relief from mental or physical pain, or gives such a sense of increased vigor and the ability to do all that the mind craves or hopes for. The effect is very intense, and, although the patient may realize the danger of relapsing, the mental impression made under the influence of the drug is so strong that the tendency to relapse is very great. The most effective treatment is the Towns treatment and the method is the same as in dealing with an alcoholic, except that the cocaine should be cut off immediately. Strychnine, with or without some form of digitalis should be given from the beginning. The belladonna mixture and from 3 to 5 cathartic pills and 5 gr. of blue mass should be given simultaneously as the first dose. The belladonna mixture is continued every hour of the day and night, and twelve hours after the initial dose the patients are again given from 3 to 5 cathartic pills followed six hours later by a saline, and at the twenty-fourth hour after the initial dose they are again given cathartics and again at the thirty-sixth hour. After these last cathartics the bilious stools appear, and by the forty-fifth to forty-eighth hour castor oil is given. Sometimes it is necessary to carry on the treatment over another period and the cathartic pills and blue mass are again given at the forty-eighth hour, which would bring the end of the treatment about the sixtieth hour. These patients should be trained physically as the morphinists, but they should be carefully looked after for a longer period.

CHAPTER XXIV

FOOD POISONING AND FOOD INFECTIONS

By ERNEST C. DICKSON, M.D.

Introduction.—The present day conception of food poisoning differs in many respects from that of twenty years ago, and much that now appears to be established is at variance with the accepted interpretations of that time. This change is in large part dependent upon the facts that modern methods of bacteriological and chemical research have opened the way to a more rational understanding of the various problems of foods and food poisoning and that investigators have devoted much time to their solution.

Not the least important result is the demonstration that ptomaines are not important factors in the causation of disease. Rosenau,[1] in this country, and Savage,[2] in Great Britain, have done much to demonstrate this fact, and various other investigators are in accord with them as to the general conclusion. Vaughan[3] states that "a ptomaine is a basic product of putrefaction and, inasmuch as it has not been demonstrated that the active agent in any poisonous food is such a body, it is manifestly incorrect and improper for a scientific man to use the words ptomaine poisoning," and Savage[2] writes "consideration of the above facts makes it most unlikely that the symptoms of food poisoning are due to any of the ordinary non-specific degradation products of the protein molecule" and "it must be accepted as certain that they (the ptomaines) play no part in food poisoning from food putrefaction." Rosenau[1] records that "a study of this subject (ptomaine poisoning) for over three years has convinced me that there is no such thing," and Jordan[4] states that it "is a diagnosis which has been made to cover a great variety of disease conditions." Too often the term "ptomaine poisoning" is synonymous with "not diagnosed," and since there is no scientific reason for its use it should be eliminated from medical nomenclature.

Nomenclature.—Interpretation of the term *food poisoning* is difficult because of the multitude of ills which may follow and be caused by the ingestion of foods. Certain members of the mushroom family and some tropical fish are inherently poisonous. The flesh of diseased animals may transmit bacterial infections or animal parasites. Foods which are derived from normal sources may become contaminated with disease-producing bacteria. Normal foods may be contaminated by metallic or vegetable poisons which gain access to them by accident or are deliberately added with criminal intent, or to preserve or improve the appearance of the product. Preserved food may contain toxic products of bacterial growth because they were not processed sufficiently to sterilize. Foods may lose their vitamine content by improper methods of preparation and cause the so-called deficiency diseases, and foods which are wholesome for the

majority of persons may cause illness of a few who are sensitized to the proteins which they contain.

It is obvious that the illnesses caused in these different ways have nothing in common excepting that they are transmitted through the medium of food, and that there is no term so comprehensive as to adequately include them all.

Accepted usage has sanctioned the application of the term "food poisoning" to include:

(*a*) Illnesses produced by the ingestion as food of substances which are inherently poisonous.

(*b*) Illnesses produced by the ingestion of foods which are contaminated with bacteria of the paratyphoid-enteriditis group. These are subclassified as "bacterial food infections."

(*c*) Illnesses produced by ingestion of foods which carry toxic products of bacterial growth. These are known as "bacterial food intoxications" and the only proved example is botulism.

Since it has been shown that, excepting those instances in which inherently poisonous substances are mistaken for wholesome food, practically all, if indeed not all, outbreaks of food poisoning are caused by certain types of bacteria or their toxic products, it is neither necessary nor desirable to classify food poisonings according to the foods which may happen to carry the infecting organism or the intoxicating agent. The symptoms of bacterial food infection of the paratyphoid-enteriditis type are the same whether the infection is transmitted through meat, ice-cream or potato-salad, and those of botulism are not at all dependent upon whether the toxin is ingested with home-canned string beans or imperfectly preserved sausage.

It has been the custom to describe outbreaks of poisoning from mussels, cheese, ice-cream, potatoes, etc., as separate types of food poisoning because the symptoms may differ somewhat from those which are usually observed, and it was believed that they were caused by some specific poison which is an inherent constituent of each type of food. It is true that outbreaks of these types are sometimes difficult to classify but the conclusion of those who have made investigations is that there is not sufficient evidence to justify a separate classification. The subject has been discussed in detail by Savage from whom the following extracts are quoted: "When mussels have caused illness it has invariably been found that they were taken from positions liable to sewage pollution" . . . "the most probable view is that the mussels become poisonous from the production in them of chemical poisons elaborated by the vital activity of bacteria derived from their sewage contaminated surroundings.

"It would appear to be probable that cheese poisoning, like other forms of food poisoning, is usually due to bacteria which produce powerful toxins."

"Ice-cream outbreaks do not differ in any essential particular from those due to consumption of other foods and there is no scientific justification for retaining them as a special group."

"The majority of the more recent investigations (of potato poisoning) suggest that the poisonous symptoms are due to bacterial activity."

In this discussion, therefore, the subject of food poisoning will be considered under three headings, poisoning by the ingestion as food of plants or vegetables which are inherently poisonous, bacterial food infections, and bacterial food intoxications.

A. POISONING BY THE INGESTION AS FOOD OF SUBSTANCES WHICH ARE INHERENTLY POISONOUS

There are many plants and a few animals which contain substances poisonous to human beings if taken into the stomach, but the number which may be mistaken for edible forms is not large. Among the plants the poisonous mushrooms are the most important but various members of the vetch family, sorrels, rhubarb leaves, etc., which contain oxalic acid, the fungus of ergot, claviceps purpurea, which attacks rye and other grains, and the roots of water-hemlock which may be mistaken for parsnips or horseradish may also cause illness in some instances.

Vetch poisoning, lathyrism, was formerly a frequent cause of illness in northern Africa and central Europe and is still found in India and other parts of Asia. There is no available record that it occurs in the United States.

Instances are recorded in which poisoning has been caused by sour-grass soup which is prepared from one of the sorrels, and from young rhubarb leaves served as greens. In one outbreak in New York City[5] it was found that poisoning was caused by sour-grass soup which contained 10 grains of oxalic acid per pint. The symptoms are those of oxalic acid poisoning.

Ergotism is rarely seen except in Russia, and is chiefly of historical interest. Ergotism and lathyrism are fully discussed by Vaughan.[3]

Poisoning from the roots of the American *water-hemlock* (Cicuta maculata L., musquash root, spotted cowbane, spotted parsley, children's bane, etc.) is probably more common than is generally believed. It is essentially a problem of the stock raiser but Pommel[6] refers to several instances in which human beings were poisoned, and Egdahl[7] collected the records of 46 human victims of whom 32 were children. Twenty-one persons in Egdahl's series died. The active principle of water-hemlock is cicutoxin (Boehm), a member of the picrotoxin group, and exists in greatest concentration in the roots. The poison is not destroyed when the roots are thoroughly boiled.

The onset of illness usually occurs in from half an hour to two hours after the roots have been eaten, but in some instances the symptoms appear while the patients are still eating the roots, and not infrequently portions of the roots may be seen in the vomitus. The most characteristic symptoms are nausea, vomiting and convulsions, although pain in the stomach may precede in some cases. Egdahl's patient became unconscious within a few minutes after the roots were eaten and had convulsions every ten or fifteen minutes. Vomiting is severe, and is followed by vertigo, slow pulse, clammy skin and unconsciousness with dilated pupils. The convulsions are epileptiform in character and may be accompanied by bloody frothing at the mouth.

Treatment.—Treatment must be instituted promptly since the progress of the poisoning is very rapid. Emesis may be induced but it is preferable to wash out the stomach through a large stomach tube until all particles of root have been removed. A full dose of castor oil should be given as soon as the stomach is empty. The patient must be kept warm with hot-water bottles, and restlessness may be controlled with bromides. Chloral hydrate or chloroform may be given for the convulsions. There is no known antidote.

Mushroom Poisoning (Mycetismus).—Mushroom poisoning appears to be increasing in frequency in the United States, presumably because of the close resemblance between the fly agaric, *Amanita muscaria*, which is widely distributed and very poisonous, and the royal amanita, *Amanita cæsaria*, which is edible. *Amanita phalloides*, the death cup, is also plentiful in many parts of the country and may be mistaken for edible forms. Ford[8] reports that there are from 70 to 80 different species of fungi which may be poisonous to man but the number which is likely to be confused with edible forms is small. Patterson and Charles[9] describe 15 edible and 5 poisonous varieties which occur in the United States and tell how they may be recognized and differentiated.

Ford[8] has classified mushroom poisoning on the basis of symptomatology and known pharmacology into the following five groups.

1. **Mycetismus Gastro-intestinalis.**—The symptoms of this type of poisoning are nausea, vomiting and diarrhœa. They vary in severity from slight nausea and painless catharsis to violent retching and purging accompanied by severe cramps in the abdomen. Symptoms terminate rapidly and usually spontaneously and the victims are well within a day or two. There are practically no fatalities except in debilitated individuals.

2. **Mycetismus Choleriformis.**—This type of poisoning is caused by *Aminita phalloides*, the death cup, and closely related forms for which there is no known antidote. Gastro-intestinal symptoms appear in from ten to fifteen hours after the fungi are eaten; they are violent and cramp-like in character and accompanied by vomiting, purging and severe abdominal pains. There is rapid loss of strength and weight, and the urine contains albumin and many casts. From 50 to 75 per cent. of the victims die, many of them in from three to five days. Necropsy shows marked degeneration of the kidney and liver tissue and of the heart muscle.

3. **Mycetismus Nervosus.**—In this group the poisoning is produced by muscarin which acts peripherally upon the parasympathetic nervous system, and is more amenable to treatment because atropine is the physiological antidote for muscarin. Violent gastro-intestinal symptoms appear early, from half an hour to two or three hours after the fungi are eaten, associated with contracted pupils, profuse sweating and salivation, convulsive movements of groups of muscles or of the whole body, and delirium, hallucinations or coma. The excitement stage is followed by symptoms of depression, the pulse becomes slow and feeble, respiration becomes labored, and death may occur from cardiac failure. The chief cause of this type of poisoning in the United States is the fly agaric, *Amanita muscaria*.

4. **Mycetismus Sanguinareus.**—In this group, which is rare, the poisoning is produced by a true hemolytic action upon the red blood corpuscles, which causes transient hemoglobinuria, accompanied by vague abdominal distress, and, in four or five days, a mild jaundice which may persist for some time. The majority of patients recover, although a few deaths are recorded. Necropsy shows evidence of extensive destruction of red blood corpuscles and marked pigmentation of the liver, spleen and kidneys.

5. **Mycetismus Cerebralis.**—Poisoning of this type is not fatal but is characterized by signs of cerebral stimulation within four or five hours after the mushrooms are eaten. The patients are exhilarated, laugh immoderately, develop a staggering gait and show disturbances of vision. The symptoms usually subside within a short time and the patients are well within from twenty-four to forty-eight hours, except for a sensation which they describe as a feeling "as if they were walking on air" and which may persist for several days.

Treatment of Mycetism.—The first indication is to obtain prompt emptying of the stomach and bowels. Apomorphine, gr $\frac{1}{20}$ to $\frac{1}{10}$ (gm. 0.003 to 0.006), hypodermically is the emetic of choice, and castor oil in full doses is preferable to saline cathartics. Administration of atropine must be regulated by the symptoms; if the onset of illness occurs soon after the fungi are eaten and the symptoms suggest the muscarin type of poisoning, atropine should be given at once and in large doses, gr. $\frac{1}{50}$ to $\frac{1}{25}$ (gm. 0.0013 to 0.0026) and repeated if necessary to obtain the physiological result. If there is inhibition of secretions or if the course of the illness suggests the phallin type of poisoning, atropine should be used with caution, and not more than gr. $\frac{1}{100}$ (gm. 0.0006) should be given.

The patients should be kept at rest in bed, and, after the bowels have been emptied, small doses of morphine may be given to relieve the pain. The extremities must be kept warm, and cardiac stimulants should be given as indicated. Blackadar[10] recommends that tannin grs. x to xv (gm. 0.65 to 1) in weak solution be given by mouth every fifteen minutes for four or five doses as a further antidote in the muscarin type of poisoning, and that normal salt solution should be administered by rectum or subcutaneously to assist elimination in the phallin type of poisoning. Ford suggests that blood transfusion should be employed when there is evidence of blood destruction.

The poisonous *animal* products are chiefly found in certain tropical fish, particularly in members of the Tetrodontidæ, the balloon or globe fish, although it is said that the roe of certain other species may become poisonous at certain seasons, and that the flesh of the Greenland shark is poisonous for dogs. There is no record that food poisoning from these sources is encountered in the United States.

B. BACTERIAL FOOD INFECTIONS

Foods may be classified as active and passive agents in the transmission of bacterial infections. They are said to play an active part when the

milk or flesh of diseased animals is used as food and transmits infection from the animal to the human being, and to be passive agents when milk, meat, vegetables, fish, shell-fish, etc., derived from normal sources become contaminated with disease producing bacteria by contact with infected food or by excretions from persons suffering from disease or who are carriers of virulent bacteria, and then transmit the infection. Bovine tuberculosis, enteriditis (Gaertner) infection and Malta fever are examples of the former group, whereas typhoid fever, paratyphoid beta infection and diphtheria illustrate the latter. All, however, may be included under the general term of "food-borne bacterial infections."

The term "bacterial food infection" has by usage been limited to those cases of acute gastro-enteritis which are caused by the bacteria of the paratyphoid-enteriditis group in which the course of the illness is characteristic and of the type which is usually described as food poisoning. There is some question as to whether *Bacillus proteus, Bacillus coli, Bacillus alkaligenes* and certain other bacteria may cause similar symptoms and should be included in this group but there is no actual proof that they are ever responsible for food poisoning.

Incidence.—The incidence of bacterial food infection in the United States is not known because relatively few of the victims are sufficiently ill to consult a physician and in the majority of the States the disease is not included in the list of reportable diseases. Moreover, it is impossible to draw accurate conclusions from mortality records because in very few of the instances in which "food poisoning" or "ptomaine, poisoning" is entered as the cause of death, has there been any necropsy examination or laboratory test to establish the diagnosis. Geiger[11] has shown that in 141 alleged outbreaks of food poisoning in which 1578 persons were ill and 85 died, investigation proved that in at least 113 outbreaks there was direct evidence that the illness was not due to food poisoning, and that in 3 of the 4 instances in which the bodies of victims were subjected to necropsy, "the original diagnosis (food poisoning) was completely refuted or changed." There is statistical evidence that the number of outbreaks of food poisoning is increasing since the mortality records show that during 1920 there were 957 deaths attributed to food poisoning as compared with 157 for 1910.[12]

Etiology.—The first of the paratyphoid-enteriditis group of bacteria was isolated by Gaertner[13] (1888) in an outbreak of food poisoning in which more than 50 persons became ill after eating the imperfectly cooked flesh of a cow which had been slaughtered because it was suffering from dysentery. Since then allied bacteria have been recovered in many outbreaks of food poisoning in many parts of the world, those which have been shown to be at fault being *Bacillus enteriditis* (Gaertner), *Bacillus suipestifer, Bacillus paratyphosus beta*, and, according to British authors, *Bacillus aertrychæ*. There are several other closely allied forms which have been isolated from the tissues or excretions of normal and diseased animals and fowls, some of which are pathogenic for their host and others apparently non-pathogenic. There is inconclusive evidence that some of these may be of importance in the causation of food poisoning of human beings. All of these bacteria belong to a group in which the various

members are very similar in morphology and cultural characteristics. It is only by careful cultural and serological tests that they can be differentiated.

There is difference of opinion as to whether the bacteria of the paratyphoid-enteriditis group produce true toxins. Clinical evidence suggests that, in addition to bacteria, there must be a toxic substance in the infected food in some instances because the onset of symptoms occurs so soon after the food is eaten that it is difficult to understand how they can be dependent upon the action of the bacteria themselves. However, experimental evidence is inconclusive. Recent experiments by Ecker,[14] Aronovitch and Rosenau[15] and Geiger, Davis and Benson,[16] indicate that toxic substances may be demonstrated in cultures of some of these bacteria, and Geiger and his associates have shown that some of them will withstand boiling for ten minutes. Rosenau reports that although the toxic substances which were obtained by Aronovitch were poisonous for guinea-pigs and mice when injected subcutaneously, they were not even irritating when administered by mouth. Moreover, the symptoms which were produced in Aronovitch's experiments did not resemble those which are characteristic of true food poisoning.

Sources of Infection.—The majority of outbreaks of bacterial food infection have been caused by foods of animal origin, particularly by those which are derived from cattle and hogs, but because human beings who are suffering from infection or who are convalescent or permanent carriers may play a part in disseminating virulent bacteria, vegetables, fish, fowl, shell-fish, etc., may become contaminated and cause the disease.

Bacillus enteriditis is a cause of disease in cattle and the majority of outbreaks of enteriditis infection in man are caused by the ingestion of milk or meat from diseased animals. Although it is probable that chronic human carriers of *Bacillus enteriditis* do not exist, persons who are suffering from the infection carry virulent bacteria in the intestinal tract, and those who are convalescent may be temporary carriers, so that it is possible that food from normal sources may become contaminated by them. It is also possible that meats may be contaminated in abbatoirs in which diseased animals have been slaughtered, or by being held in storage with contaminated meat, but this cannot often happen if proper hygienic precautions are enforced.

Bacillus suipestifer is often found as a secondary invader in hogs which are suffering from hog cholera. Some of the German authors believe that this form is identical with *Bacillus paratyphosus beta*, but British and American investigators agree that they may be differentiated by serological tests. A few cases of human infection have been traced directly to diseased hogs but the majority of outbreaks in Great Britain have been attributed to a strain which may be transmitted by human carriers and which is called *Bacillus aertryche*. Since human carriers play a part in the dissemination of this organism, outbreaks of infection may be caused by foods other than those of animal origin.

Some investigators, including Savage,[2] believe that all outbreaks of food infection are caused by *Bacillus enteriditis* or *Bacillus aertryche*, and that *Bacillus paratyphosus alpha* and *beta* are always associated with

illness which is of the type of typhoid fever. Other authors, however, attribute some outbreaks of typical food infection to *Bacillus paratyphosus beta*, and instances are recorded in this country, in Great Britain and in Europe in which this organism was recovered from the stools of patients with food infection. *Bacillus paratyphosus beta* has not been found in animals but occurs only in human beings who are suffering from the infection or who are convalescent or chronic carriers. Outbreaks of infection, therefore, are dependent upon contamination of food from human excreta and may be caused by any kind of food in which the bacteria will survive and multiply.

In the majority of instances outbreaks of food infection have been caused by foods which were uncooked or imperfectly cooked. All the bacteria of the paratyphoid-enteriditis group are relatively susceptible to heat and thorough cooking of the food will destroy them, but it has been shown that in some instances the amount of heat which penetrates to the centre when cooking an article of food may not be sufficient to sterilize it. It is therefore possible that outbreaks may occur from food which is thought to be thoroughly cooked.

Many instances are recorded in which illness has developed after the consumption of raw or imperfectly cooked food whereas no illness occurred when portions of the same food had been thoroughly cooked. There are other instances, however, in which no illness followed the ingestion of freshly-cooked food but typical food infection was caused by eating the left-over portion of the food some days later. This may have been due to the fact that the food was imperfectly cooked and a few bacteria survived but were not sufficiently numerous at first to overcome the natural resistance of the body, whereas after a few days incubation they had become so numerous as to cause illness. It is also possible that after the food was cooked it was contaminated by a carrier or by contact with other contaminated food, and then transmitted the infection. It has been noted that finely divided foods, such as chopped meat, in which there is facility for the rapid dissemination of bacteria, are especially liable to be the cause of this late poisoning.

Seasonal Distribution.—The majority of outbreaks of bacterial food infection occur during the summer months when the temperature is more favorable for bacterial growth.

Pathology.—There is no characteristic change in the tissues which is pathognomonic of bacterial food infection. The most frequent demonstrable lesions are hyperemia and œdema of the gastro-intestinal mucous membrane with minute hemorrhages in the walls of the tract, and parenchymatous degeneration of the liver and kidneys. Microscopic examination may show swelling and desquamation of the epithelial structures of the mucosa and round-cell infiltration and minute hemorrhages in the wall. It is not uncommon, however, to find relatively minute pathological changes in cases which had run a violent clinical course.

Symptoms and Course.—Bacterial food infection is characterized by a sudden onset of acute gastro-intestinal disturbances with relatively low fever and marked prostration. The duration of serious illness rarely exceeds two or three days although convalescence may be prolonged

because of weakness. The mortality-rate is very low, probably less than 1 per cent.[12]

The onset usually occurs in from six to twelve hours, but instances are recorded in which the onset occurred within half an hour, and others in which there were no symptoms for more than thirty-six hours after eating the infected food. In the instances in which signs of poisoning appear very soon after the infected food is eaten the clinical evidence seems to justify the hypothesis that the food contains bacterial toxin at the time it is consumed.

There is marked variation in the severity of the symptoms in different outbreaks of the infection and among different individuals in the same outbreak. Some are only slightly indisposed, not sufficiently so to cause them to cease work, whereas others may become violently ill with severe gastro-enteritis, pass into a state of collapse and succumb within from twenty-four to forty-eight hours. The average case is one in which the illness reaches its maximum within twenty-four hours and subsides within two or three days.

Pain in the abdomen may be the first symptom although sometimes the victims complain first of headache and chilly sensations, occasionally with rigors. The pain is usually colicky in character and there may be diffuse tenderness in the abdomen. The abdominal muscles may remain soft or there may be localized or general rigidity. Sometimes the maximum rigidity and tenderness are in the region of the cecum, simulating acute appendicitis. The spleen may become enlarged and palpable within two or three days after the onset. *Diarrhœa* is the most constant feature and may or may not be associated with nausea and vomiting. The stools are semi-fluid and offensive at first but soon become watery and greenish in color. In severe cases they may contain fresh blood. Tenesmus may be very distressing. *Nausea* and *vomiting* are less constant but occur in the majority of cases, and may be very severe. In some instances the vomitus contains fresh blood. Excessive thirst is practically constant.

Fever is inconstant. In mild cases the temperature may remain normal but in the typical case of moderate severity it begins to rise soon after the onset of gastro-intestinal disturbances, reaches its maximum of from 102° to 104° F. within twenty-four hours and gradually subsides to normal within from three to five or six days. Sometimes the course of the illness is greatly prolonged and the fever persists for many days as in typhoid fever. It is believed by some that in such instances the bacterial infection has ceased to remain localized in the intestinal tract and has become general, associated with septicemia. In severe acute cases in which the patient passes into collapse the temperature may drop suddenly below normal and cold perspiration may appear as in traumatic shock. In mild cases the *pulse-rate* may remain within normal limits but in severe cases it becomes much more rapid than is explained by the degree of fever. In cases with collapse it is identical with that observed in shock.

In some instances there is severe *erythema* or *urticaria* followed by desquamation, and in others, *herpes labialis* have been described. Not infrequently the patients complain of tenderness and cramps in the muscles of the extremities.

Nervous manifestations vary in proportion to the intensity of infection. In mild cases they may be absent or very slight but when the infection is of moderate severity the patients may be restless, apprehensive and unable to sleep, and in more acute infections they may be delirious. Convulsions are common in children and the majority of victims suffer from headache. A most striking effect is that, even when the infection is not severe, there is early and pronounced prostration which may persist for days after the fever has subsided and which is in large part responsible for the prolonged convalescence.

No characteristic changes in the blood picture have been described; the leukocyte count may remain about normal and there is no rapid destruction of red blood cells. Specific agglutinins may be demonstrated in the blood serum after the first five or six days of illness, but may not be found in milder cases. Blood cultures have been reported positive only in those instances in which the course of the disease was like that of typhoid fever.

The urine usually contains albumin and casts, and the amount is diminished when there is vomiting and diarrhœa.

It is impossible to make a diagnosis from the appearance of the stools but bacteriological examination may reveal the presence of bacteria of the paratyphoid-enteriditis group. Sometimes when the infection is due to *Bacillus paratyphosus beta* or *Bacillus aertryche* the virulent bacteria remain in the gastro-intestinal tract for many months after the patient has recovered, but it may be necessary to make repeated cultures of the feces before they can be demonstrated.

Diagnosis.—The diagnosis of bacterial food infection can be established only by laboratory methods, and, excepting in group outbreaks in which epidemiological evidence is such that there can be no doubt, the diagnosis should not be made until the laboratory tests have proved that bacteria of the paratyphoid-enteriditis group are at fault. The signs and symptoms may be closely simulated by acute abdominal conditions such as appendicitis, cholecystitis, perforating gastric ulcer, etc., by certain intra-thoracic processes such as diaphragmatic pleurisy or angina pectoris and, especially in children, by any of the acute infectious diseases. It has been suggested by Harris[17] that the incidence of abdominal pain associated with constipation is evidence that the illness is not food poisoning, but this is not always true because there are acute abdominal conditions which are accompanied by diarrhœa, and victims of botulism may complain of abdominal pain associated with constipation.

A carefully taken history in which inquiry is made as to the condition of other persons who have been associated with the patient at each of several meals prior to the onset of his illness, may supply the information which leads to diagnosis. In group outbreaks in which several persons develop similar symptoms at about the same time there is usually little difficulty in obtaining presumptive evidence that food poisoning is at fault and in determining the source of the infection, but when only one person is ill the problem is much more difficult and even though it is possible to prove that the patient has eaten some food which was not shared with others, the probability is great that his illness is caused by some other disease than food infection.

Treatment.—Bacterial food infection is a disease of limited duration and the majority of patients recover promptly, but, although persons who show a mild reaction require little or no attention, those with more severe infection demand early and active treatment. Such patients should be kept quiet in bed but unless they are in a condition of shock should not receive morphine or any of its derivatives until after the gastro-intestinal tract has been emptied.

The stomach should be thoroughly washed and rewashed, preferably through a large stomach tube with openings in the side as large as the diameter of the lumen, in order that all particles of food may be removed. Plain warm water may be employed although some prefer boric acid solution, 1 tablespoonful to the gallon, or sodium bicarbonate solution, 2 teaspoonfuls to the gallon. If a suitable stomach tube is not available large draughts of warm water containing sodium bicarbonate or sodium chloride may be given to induce emesis, and should be repeated until no food particles return. Thorough washing is preferable to induced vomiting by apomorphine, or the usual emetics, and should not be omitted even when the patient has been vomiting.

After the stomach has been emptied full doses of castor oil or of magnesium sulphate in concentrated solution should be given, preferably through the stomach tube before it is withdrawn. The colon should be thoroughly flushed with warm water or with simple enemata, even though there has been diarrhœa, and this should be repeated at frequent intervals.

Nausea and vomiting may cease after lavage, but, if they persist, may be relieved by the administration of small quantities of bland liquids at frequent intervals, 1 teaspoonful of barley water or albumin water every fifteen or thirty minutes, or by the application of a mustard plaster or an ice-bag over the epigastrium. Turpentine stupes, a large mustard plaster over the whole abdomen or a hot-water bottle may relieve the pain.

Diarrhœa which persists after the bowels have been emptied may respond to bismuth subnitrate or subgallate, gr. xv (gm. 1) every one or two hours, but it may be necessary to administer paregoric in dram doses every hour for several hours.

In the milder infections it may be that sufficient water can be taken by mouth or absorbed from the bowel to relieve the thirst, but in severe infections these methods of administration are not tolerated. In some instances cracked ice can be sucked without inducing vomiting and in this event it should be given freely. More often in severe cases, it is necessary to give normal salt solution subcutaneously or by intravenous injection, preferably by the former method.

Patients in whom there are evidences of collapse should be treated as for traumatic shock. They should be wrapped in warm blankets, hot-water bottles should be applied and fluids should be administered. Lavage and colonic irrigations with warm water are especially indicated in these cases, particularly if it has been necessary to prescribe opiates, because, in addition to emptying the gastro-intestinal tract, they permit of the application of heat internally and afford opportunity for the absorption of fluids.

Medication must be as indicated. Caffeine is the stimulant of choice, and, if the patient can retain it, may be given in the form of strong black coffee; otherwise caffeine citrate should be given hypodermically, gr. ii (gm. 0.13) every four hours or as required. Camphor in oil may be given in emergency, and some give strychnine in full doses, although it is probable that this is preferable during convalescence.

Barley water and thin gruel may be given as soon as they can be tolerated but it is said that milk should be avoided because it affords suitable medium for bacterial growth. A return to solid food should be very gradual and only after all acute symptoms have subsided. In some cases the secretion of hydrochloric acid in the stomach is impaired and it is necessary to give dilute hydrochloric acid after meals. If the illness has been very severe and prostration and weakness are pronounced, convalescence may be hastened by the use of simple tonics.

C. BACTERIAL FOOD INTOXICATION

Bacterial food intoxication is here considered to be synonymous with botulism because botulism is the only type of food poisoning in which it has been proved that a bacterial toxin is the cause of the poisoning. The toxin is produced by the growth of *Bacillus botulinus* in preserved foods and is extremely poisonous for different species of animals and fowls as well as for man. It has been shown to be a cause of forage poisoning of domestic animals, expecially of horses and mules, and of limber-neck of chickens, turkeys and ducks. There are also records of poisoning of wild animals and birds.[18]

Incidence.—The first recorded outbreak of botulism was described in 1735 and since the early part of the nineteenth century there have been many outbreaks in various parts of Europe. In the early German literature the term botulismus was used synonymously with Wurstvergiftung, sausage poisoning (botulus means sausage) but by the middle of the century it was recognized that other kinds of preserved meats or fish might cause the same type of poisoning.[19] In 1894, van Ermengem,[20] in Belgium, demonstrated that botulism is caused by a bacterial toxin and since that time the term has been applied to all outbreaks of poisoning in which botulinus toxin is at fault, regardless of the type of food which contains the toxin or of whether human beings, animals or fowls are the victims.

The majority of the recorded outbreaks of human botulism in Europe occurred in Germany, especially in south Germany, but cases have been described in almost all the adjoining countries,[19] and there has been one serious outbreak in Great Britain.[21]

Prior to 1902 the American medical literature contained no reference to outbreaks of botulism in the United States although several outbreaks which were described as ptomaine poisoning were probably botulism.[19] Since then a number of outbreaks have been recognized in this country and during the past ten years the interest in botulism has been such that it is probable that the majority have been recorded. During the period from 1904–1923 inclusive there were 126 recorded outbreaks of botulism

in the United States, and 1 in the Yukon Territory in Canada, in which human beings were poisoned. The patients numbered 429, of whom 280 died. The mortality-rate was approximately 65 per cent.[18] Since 1914 the majority of human outbreaks have been proved by the demonstration of *Bacillus botulinus* or its toxin.

Etiology.—*Bacillus botulinus* is a spore-bearing, toxin-producing organism which is classified as anaërobic. It is widely distributed in Nature in the soil, occurring in the virgin soil of high mountains as well as in the richly fertilized soil of cultivated valleys, but its normal function in the soil is not known. It has been demonstrated in specimens of soil from many parts of North America, Europe, Great Britain and the Hawaiian Islands.[22]

The organism thrives in mediums prepared from meats, fish and many kinds of vegetables and fruits, and it grows well and produces virulent toxin at the usual atmospheric temperature as well as at the temperature of the body. It is usually classified as anaërobic but grows abundantly in mediums which are only partially anaërobic and is sometimes found under practically aërobic conditions in symbiosis with vigorous aërobic bacteria and yeasts.

Large number of subterminal *spores* are formed when the organism grows in suitable environment. The majority of the spores are destroyed by exposure to moderate degrees of heat but some are very resistant, surviving six hours exposure in neutral broth at the temperature of boiling water at sea level, and ten minutes in brain medium heated to the temperature of 10 pounds steam pressure (115° C.). The resistance is greater when the spores are heated in mediums of approximately neutral reaction and becomes rapidly less as the medium becomes more acid or more alkaline. There is a marked increase in the survival time when a thin layer of oil covers the surface of the medium in which the spores are heated, which is of considerable importance in the canning of certain types of food.[23]

When botulinus spores are placed in a suitable medium under conditions favorable for growth, the majority of them germinate promptly, but a few, like the seeds of certain legumes, remain dormant for varying periods of time. The dormancy occurs in spores which have not been damaged by heat[24] as well as in those which have been heated, but appears to be more prolonged in heated spores. The maximum dormancy which has been demonstrated in heated spores is twenty-two months in plain broth and thirty-seven months in broth which is covered with a thin layer of oil.[25] When dormant spores eventually germinate they produce vegetative growth which appears to be as vigorous as that from spores which germinate promptly.

Botulinus toxin is a true exotoxin. It differs from tetanus and diphtheria toxins in that it is not destroyed by the action of the digestive ferments but is absorbed unchanged from the gastro-intestinal tract. Under experimental conditions it has been shown that poisoning with identical symptoms is produced when the toxin is placed in the stomach, injected under the skin, into the muscles, into the body cavities or into the blood stream, or rubbed into scarified areas in the skin. The toxicity

for human beings is such that the amount of toxin contained in a small fragment of a bean pod from an infected jar is sufficient to cause the death of an adult.

The toxin is a protein substance which may be precipitated by alcohol or neutral salts but its chemical formula is unknown. It is relatively unstable when in solution but is very stable in the dried form. It is rapidly destroyed by exposure to heat although the length of time required to detoxify infected food depends upon the character of the food. Exposure of all portions of the food to the temperature of boiling water for from seven to ten minutes is sufficient to destroy the toxin, but due allowance must be made for the penetration of the heat into the more solid portions of the food.

In laboratory experiments it has been possible to cause botulinus intoxication in small animals by the administration of enormous numbers of detoxified botulinus spores into the stomach or by subcutaneous injection, but there is no record that human botulism has ever been caused by the production of toxin within the body. In every known human outbreak the botulinus toxin was produced in the food before it was consumed and was ingested with it.

Three types of botulinus toxin have been described as Types A, B,[26] and C,[27] respectively, and for each of these a specific antitoxin may be produced. The antitoxin of each, however, affords protection against homologous toxin only, and does not protect against the toxins of other types. In all instances the antitoxin is effective when it is administered soon after the toxin but has little protective action if its administration is delayed until after symptoms of poisoning have developed. The majority of human outbreaks have been caused by Type A toxin, and, insofar as is known, none has been caused by Type C.

Sources of Poisoning.—Human botulism is always caused by the consumption of preserved food in which the process of preservation has failed to destroy botulinus spores which had gained access to the raw food material or to the containers. If other putrefactive bacteria are associated with *Bacillus botulinus* in the food, spoilage is usually so unmistakable that there is little danger of the food being consumed, but when the food contains only botulinus spores the signs of spoilage may be so slight as to escape recognition unless the individual who serves the food is on the alert.

The appearance of the container with its bulging ends or signs of leakage, the loose tops of containers which are sealed by vacuum or the escape of gas under pressure, instead of suction, when the container is opened should attract attention, and the recognition of discolored or softened areas in preserved meats may arouse suspicions of spoilage. Usually there is an odor like that of rancid butter or certain kinds of cheese but sometimes this is masked and does not become apparent until the contents of the container are disturbed or heated. Solid portions of the food may become soft and the liquor may be cloudy, but not infrequently the appearance of the food shows little change from normal. If such food is served as salad with mayonnaise or vinegar any unusual taste or odor may be masked and escape notice.

With but three recorded exceptions, all known outbreaks of botulism in Europe have been caused by the ingestion of spoiled preserved meats or fish, but in the American continent the great majority, almost 80 per cent., have been caused by preserved vegetables and fruits. This is undoubtedly due to the fact that in America there is relatively little consumption of uncooked preserved meats whereas many preserved vegetables and fruits are eaten without being cooked after they are removed from the containers.

Home-canned products have been responsible for 67 of 98 outbreaks in which the cause of poisoning was ascertained, string beans, corn and asparagus heading the list for home-canned products, and spinach and ripe olives having caused the majority of outbreaks from commercially-canned foods. Other preserved foods which have been responsible are beets, apricots, pears, chile-sauce, bottled clam broth, fish, chicken, ham, sausage and cottage cheese.

Seasonal Distribution.—Since botulism is produced by preserved foods, the incidence is in part independent of season. In rural communities, where there is a dearth of fresh vegetables during the winter months, there is a greater incidence of botulism at that time, but in urban districts outbreaks may occur at any season.

Pharmacology and Pathology.—Experiments have shown that botulinus toxin does not act centrally upon the nervous system but that it affects the peripheral endings of certain nerves. The most marked effect appears to be exerted upon the parasympathetic fibres of the third, seventh, ninth and tenth cranial nerves, and of the pelvic nerves, which constitute the prenuclear and bulbo-sacral outflows of the autonomic nervous system.[28] The effect upon these nerves is to block the passage of nerve impulses to the structures which they supply, thereby simulating paralysis, but there is no true paralysis because the continuity of the nerve mechanism remains intact and a nerve impulse of sufficient intensity will temporarily reëstablish function. An effect of less intensity is exerted upon skeletal motor nerves, resulting in a susceptibility to fatigue[29] which has been described by Edmunds and Long[30] as a "curare-like" effect. In skeletal muscles, as in involuntary muscles, there is no true paralysis. No disturbances of function have been noted in structures supplied by nerves of the sympathetic system.

At necropsy there may be more or less marked congestion of the central nervous system, particularly around the base of the brain, and there may be hemorrhages in the meninges and serous membranes. Congestion of the lungs and abdominal viscera, and cloudy swelling of the parenchymatous organs are practically constant, and there may be bronchopneumonia.

Microscopical examination of the tissues confirms the presence of hyperemia, hemorrhages and parenchymatous degeneration. There may be thrombi which are studded with leukocytes in the vessels of the central nervous system as well as in the organs of the trunk, but they are probably agonal in origin and are not pathognomonic of botulism. In fact, there is nothing in the gross or microscopical appearance of the tissues by which botulism can be diagnosed.

Symptoms and Course.—The typical case of botulism differs from one of other types of food poisoning in that there is a delayed onset, absence of acute gastro-intestinal disturbances and absence of fever. It is characterized by disturbances of vision, marked weakness of skeletal muscles, persistent constipation and absence of sensory disturbances. The characteristic clinical picture is that of severe intoxication and not of infection.

In about one-third of the cases described in America there has been early gastro-intestinal disturbance, occurring for half an hour to a few hours after the poisonous food was eaten and ranging from a sensation of distress in the stomach to severe nausea, vomiting and diarrhœa. These symptoms may subside within a few hours but usually persist for twenty to thirty hours until they are replaced by the typical botulism symptoms. There is no associated fever and it is probable that the gastro-intestinal irritation is produced by the local action of the spoiled food in which the botulinus toxin is conveyed to the stomach and not by the toxin itself.

In the majority of instances the patients show no signs of illness for from eighteen to thirty-six hours after the toxin is swallowed, and instances are recorded in which several days elapsed before symptoms of poisoning appeared. When illness occurs earlier than fifteen hours after the poison is ingested it is usually of the acute gastro-intestinal type which has been described.

The first indication of illness may be an indefinite feeling of lassitude or fatigue, which, in typical cases, may be ascribed to the coincident constipation. Soon, however, the patients complain of progressive weakness, incoördination of muscular movements, disturbances of vision and difficulty in swallowing and in talking.

Disturbances of *vision* may include blepharoptosis, mydriasis, diplopia, loss of reflex to light, loss of accommodation for near vision and, occasionally, nystagmus. When the dilated pupils are not covered by the drooping upper eyelids there may be photophobia. There is no actual destruction of the retina although the vessels may be much congested. The patients can usually see distant objects clearly with either eye alone.

Difficulty in *talking* appears to be caused by fatigue of the muscles of articulation since speech becomes progressively less intelligible when the patient persists in attempting to talk. The first words with which there is difficulty are those in which movements of the tongue are important.

Difficulty in *swallowing* is largely due to incoördination and fatigue of the muscles of the tongue and pharynx, and patients state that they have no difficulty in swallowing food if they can get it back into the gullet. It may be that dryness of the mouth plays some part, because patients who are not severely poisoned may be able to swallow solid food if they take water at frequent intervals. In severe cases the patients are unable to swallow liquids or solids, and fluids are regurgitated through the nose when they attempt to do so.

Movements of the tongue become slow and patients may have difficulty in raising the tongue over the teeth to protrude it. The muscles are relaxed so that it looks and feels larger than normal, in fact, patients often complain that the tongue feels too big for the mouth. The surface is usually coated with thick brown fur.

There is inhibition of the serous portion of the saliva but the mucus portion is excreted in a thick, tenacious form which is dislodged with difficulty. The result is a dryness of the mucous membranes of the mouth and accumulation of thick mucus in the pharynx which is most distressing. Severe strangling spells are often induced by attempts to clear the pharynx or to swallow and may result in insufflation bronchopneumonia.

Severe *constipation* sets in early and is most persistent, all efforts to induce evacuation of the bowels being usually unsuccessful. The inhibition of peristalsis involves the movements of the stomach as well as those of the intestines with the result that food may remain in the stomach for several days.

Weakness of the skeletal muscles is very characteristic and when sustained muscular effort is required to maintain the normal position of a part, for example the upper eyelid in man and the head in animals and fowls, failure to maintain that position is one of the early signs of intoxication. It is often said by persons who are not severely poisoned or in whom the symptoms of poisoning are just beginning, that although they can balance the head in the upright position so long as they remain erect they are obliged to support it with the hand if they bend forward. The victim of severe intoxication lies relaxed in bed, as if under general anesthesia, and, although he may raise an arm or a leg once or twice, or may open the eyes a few times, he soon becomes so fatigued that he cannot repeat the act. The muscles become soft and flabby, but there is no rapid onset of atrophy as in acute poliomyelitis and the peripheral reflex arcs remain intact.

Botulinus intoxication is characterized by the absence of sensory or mental disturbances. In some instances there may be headache or dizziness at the onset, and occasionally there is pain in the abdomen, but usually the patient is free from pain. Many of the victims are apprehensive and some become hysterical, particularly in the early stage of the illness, and often they are unable to sleep. Some become very irritable when they are aroused or are unable to make themselves understood, but it is very seldom that they become comatose or delirious. One of the most striking and distressing features is that until the circulation and respiration begin to fail the victim remains fully conscious and aware of the seriousness of his condition.

In uncomplicated cases the *temperature* remains normal or subnormal but it responds in the usual manner when bronchopneumonia or other infections supervene. The pulse may be somewhat slow at first but soon becomes very rapid. In severe cases it is not unusual to observe a pulse of 120 or more when the temperature lies between 96° and 98° F.

Respiration may be unimpaired in the early stages of intoxication, although there may be undue acceleration following slight exertion. As the intoxication progresses, respiratory movements become more rapid and more labored until toward the end there may be partial asphyxia and all the accessory muscles of respiration are brought into play. Cheyne-Stokes breathing may be observed and during strangling spells the patient may become very cyanotic, in fact death may occur during a strangling spell. Respiratory failure is the most frequent immediate cause of death.

The *duration* of illness varies considerably. In a series of 196 fatal cases in the United States, 1 person died within twenty-four hours and 142 died in from two to five days after ingestion of the toxin. The number of deaths within three days is somewhat greater than is recorded in Germany, but in general the evidence here supports the view of Müller[31] who stated that the majority of victims die in from four to eight days after the poisonous meal and that, unless bronchopneumonia supervenes, few die who have survived for ten days.

Death usually is due to respiratory or cardiac failure and it has often been noted that the heart may continue to beat for several minutes after respiration has ceased. At times, however, the patient appears to be recovering from the effects of the intoxication but eventually succumbs to bronchopneumonia.

When recovery occurs convalescence is very slow and tedious. Improvement in talking and in swallowing and cessation of strangling spells may be the first indications of recovery, and may begin by the end of the first week in moderately severe cases. Disturbances of vision and muscular weakness persist much longer and may be far from normal for several months. One patient, six months after his illness, was still weak and underweight, with low blood-pressure and little resistance to fatigue. He eventually recovered his former health.

Diagnosis.—Botulism is always caused by spoiled preserved food and the onset of symptoms may be delayed for from eighteen hours to several days after the food was eaten. It is necessary, therefore, when botulism is suspected, to make careful inquiry concerning all preserved foods which may have been consumed or tasted during several days preceding the onset of symptoms. It may be that by so doing it will be possible to establish that the patient is but one of a number of persons who were poisoned at the same time. Single case outbreaks of botulism are more frequent than single case outbreaks of other forms of food poisoning because of the fact that housewives often taste spoiled food when they open the containers. The history of having done so or the coincident illness of chickens which have eaten the spoiled food may aid in diagnosis.

It is not possible to diagnose botulism during the interval which elapses between the ingestion of poison and the onset of typical symptoms, and it is during this period that acute gastro-intestinal disturbances may cause one to suspect food infection or some intra-abdominal inflammatory process. The absence of fever and a normal leukocyte count should arouse suspicion, and the later onset of disturbances of vision and difficulty in talking or swallowing should suggest botulism.

There is little in the clinical laboratory tests which are of value in diagnosis. There is nothing characteristic in the urine although the amount may be greatly diminished because of the inability of the patient to swallow liquids. The red blood cell count may show a relative increase because of the partial dehydration but the leukocyte count remains within normal limits unless there is coincident infection. The cerebrospinal fluid shows no characteristic change and the blood-pressure remains unchanged. Sometimes it is possible to demonstrate botulinus toxin in the blood of the victims by injecting 1 cc. of blood serum into the peritoneal cavity of a white mouse, but this is not at all constant.

If portions of the poisonous food or specimens of vomitus are available and if one has a supply of botulinus antitoxin of the various types, it is possible to establish a diagnosis and to determine the type of the toxin within a few hours by the injection of laboratory animals. A small amount, 1 cc., of the liquid portion of the food or vomitus, or of a saline infusion of the solid portions, should be injected subcutaneously or into the peritoneal cavity of each of four guinea-pigs or white mice, or into the ear vein of each of four small rabbits. One animal of the series should be kept as a control but the other three should receive injections of botulinus antitoxin, Types A, B and C respectively. If botulinus toxin is present in the food or vomitus, the control animal and those which received the heterologous antitoxins will succumb within twenty-four to thirty hours whereas the one with homologous antitoxin will survive.

It may be possible to isolate *Bacillus botulinus* from the suspected food or from the vomitus or feces of the victim, but this requires several days and is of no value for immediate diagnosis.

The disease processes which are most liable to be confused with botulism are belladonna poisoning and epidemic encephalitis, although cerebrospinal syphilis, acute poliomyelitis and certain toxic ophthalmoplegias must be considered. The absence of fever and the normal cerebrospinal fluid should differentiate from encephalitis and cerebrospinal syphilis and the absence of flaccid paralysis from poliomyelitis. Belladonna poisoning most closely simulates botulism but can usually be excluded by the history. The excitement and delirium of belladonna poisoning are rarely, if ever, observed in botulism.

Treatment.—One of the typical effects of botulinus intoxication is the development of susceptibility to fatigue and instances are recorded in which persons, who appeared to be only slightly poisoned and who refused to rest in bed, succumbed, whereas others, who were more seriously ill, at first, remained in bed and recovered, Even the exertion caused by moving a patient in an ambulance or turning him in bed has resulted in sudden death although his condition had appeared to be fairly good. It is therefore necessary to protect the patient from all unnecessary excitement and fatigue, and he should be kept in bed and as secluded as possible, even if he does not appear to be seriously ill.

If he is seen early, before difficulty in swallowing or strangling spells have begun, it is advisable to wash the stomach through a stomach tube and to place castor oil or magnesium sulphate in saturated solution in the stomach before the tube is withdrawn. If the patient is seriously ill, particularly if he is having strangling spells, it is very doubtful whether the benefit to be derived from emptying the stomach offsets the damage which is caused by fatiguing him. One patient was observed in whom attempts to pass a stomach tube induced an attack of strangling in which he died. The use of emetics is not recommended because of the danger of inducing strangling and insufflation.

The colon should be thoroughly flushed with simple soap-suds enemata, repeated at as frequent intervals as possible without causing undue fatigue. Pituitrin has been recommended by some authors but does not always produce evacuation of the bowels.

Restlessness and insomnia should be controlled by bromide in full doses if the patient can swallow or by subcutaneous injections of morphine *without atropine*, if he is unable to do so. Bronfenbrenner and Weiss[32] recommend that the patient should be kept well under the influence of morphine during the whole course of illness in order to inhibit response to outside influences, and thereby prevent fatigue, but the efficacy of this measure has not been proved. The effect of the morphine upon the respiration must be closely watched if it is given.

If botulinus *antitoxin* is available it should be given as soon as possible after the diagnosis is made or seriously considered because it is of little value unless administered very early. In fact, it is exceedingly doubtful whether it will affect the course of illness in victims in whom the symptoms have become well established but it may be of value in other persons who have been exposed to the poisoning but who are not yet seriously ill. The antitoxin should be injected into the veins after the usual tests for sensitization to horse serum have been applied, and the patient desensitized if necessary. One or two large doses, at least 20,000 units for an adult, are preferable to repeated small injections, and, unless the type of toxin has been ascertained, a polyvalent antitoxin or a mixture of the various types of antitoxin should be used. The majority of outbreaks of human botulism in the United States have been caused by Type A toxin.

The patient should receive nourishing but easily digested food if he can swallow, but the duration of serious illness is short and it is better to have him abstain from food than to run the risk of strangling and insufflation by urging him to swallow. If he can tolerate the stomach tube, food and water may be administered through it, but usually it is necessary to give liquids by the bowel or subcutaneously.

The accumulation of thick mucus in the pharynx causes much discomfort and tends to induce strangling. It should be removed at frequent intervals by means of a soft swab or by gentle suction through a soft rubber catheter attached to an aspirating bottle in which a slight negative pressure is maintained. The mouth should be kept as moist as possible with a suitable mouth wash and, if it does not induce strangling, the patient may suck cracked ice, preferably wrapped in gauze, to prevent it from falling into the pharynx.

Medication is non-specific and is of little value, but distressing symptoms should be treated as they arise. Theoretically, members of the pilocarpine group should counteract the effect of botulinus toxin but practically they have not proved satisfactory. Pilocarpine has been tried in doses as large as 20 drops of a 1 per cent. solution daily, but it has given only very temporary relief and has produced pulmonary œdema which apparently hastened death. Cholin derivatives have been tried in animals without any appreciable result, and eserine has been used without effect.

Caffeine citrate, gr. ii (gm. 0.13) by hypodermic injection or hypodermic preparations of digitalis may be used for cardiac failure, but usually this is terminal and not affected by therapy. Strychnine may be beneficial and should be administered freely, gr. $\frac{1}{30}$ (gm. 0.002) every four hours,

unless signs of muscle irritability are noted. Especial care should be exercised if the patient is also receiving morphine. *Atropine is contra-indicated* because its effect in many ways is similar to that of botulinus toxin. Alcohol is probably of no value as a preventive or therapeutic agent.

Because the intoxication is of limited duration and there is no new formation of botulinus toxin in the body, every effort should be made to sustain the patient until its effect has subsided. Oxygen should be administered when respiration becomes labored and everything should be ready to apply artificial respiration when voluntary respiration ceases. Human patients have been kept alive for several hours[19] and Edmonds and Keiper[33] report that dogs have been kept alive for more than twenty-four hours after voluntary respiration had ceased.

During convalescence the patients should be given nourishing food as soon as they can swallow and kept from over-exertion until they have regained their strength. Tonic treatment with arsenic and nux vomica may be of value but iron is not usually indicated.

When bacterial food infection or food intoxication is suspected, the aid of a competent bacteriologist should be obtained as soon as possible, and remnants of suspected food and specimens of vomitus and stools should be preserved in order that there may be no delay in performing the laboratory tests. If local laboratory facilities are not available, the municipal or state laboratories should be notified, and their assistance solicited. Although in many States food poisoning is not included in the list of reportable diseases, it is advisable to notify the health authorities whenever such outbreaks occur in order that they may assist in establishing the diagnosis and have a record of the actual incidence of food poisoning in the community.

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PART VII

DEFICIENCY DISEASES

CHAPTER XXV

PELLAGRA

By EDWARD JENNER WOOD, M.D.

Synonyms.—Mal de la rosa, flema salada, mal del monte, calor del Higado, mal del Higado, pellarina, scottaturo di sole, calore del fegato, mal della spienza, scorbuto montano, maladie de la Teste, pellagra des Landes, mal d'Aerouse, mal de Bascons, mal de Saint Amans, mal de Saintes-Rosa, mal des Saintes-Mains, lepra endemica. In recent years in Barbadoes the disease, not recognized as pellagra, was designated psilosis pigmentosa. This list is important only in searching the literature for the earlier accounts as most of these names have ceased to be used.

Pellagra is a disease occurring chiefly in chronic form though occasionally in an acute fulminating form. It is more prevalent in warmer climates but has been found in every part of the world in recent years. It is characterized by symptoms referable to the skin in the form of symmetrical erythema or dermatitis chiefly of the exposed parts of the body; by symptoms referable to the digestive tract, chiefly as stomatitis and diarrhœa, and by nervous and mental changes. It is a disease of very definite seasonal variations appearing in the warmer months and usually abating in winter.

History.—The first authentic account of pellagra was that of Gaspar Casal, in 1735, which was not published until 1762. His description is given under the name mal de la rosa but he made no claim to having originated it. In 1775 Zanetti reported the appearance of the disease on the shores of Lago Maggiori stating that it was vulgarly called pellagra and attacked the poor and malnourished. Throughout this period there was much confusion of pellagra with scurvy which explains the term, alpine scurvy.

The appearance of pellagra in the United States about 1907 renewed interest in the mystery of its age. This was a point of more than historical interest at the time for it was involved in the study of etiology. At that time the ancient and generally accepted theory of causation connected Indian corn or maize with the disease and the American observers unhampered by tradition were unwilling to accept the maize theory without

full justification. Maize had been the chief cereal food in many sections of the southern states and pellagra had certainly not existed to any considerable extent. If pellagra were a disease of antiquity it must have occurred in Europe before the introduction of Indian corn from America. Pellagra was probably widely prevalent in Spain in the sixteenth and seventeenth centuries because it appears to have been recognized in Italy by Spaniards from Galicia, the Asturias, New Castille and Aragon. Sambon found in Pliny's Natural History a striking account of the disease occurring in the days of Tiberias. In this account the disease is recorded as occurring in Spain, Italy, Gaul, Illyricum and Egypt. It is interesting that these countries still suffer from it.

In the accounts of the "epidemie de Paris" of 1828 one observer noted that the condition was identical with that described by Thomas Jordanus as *nova luis* and as *luis Gallica* which occurred in epidemic form in the town of Brünn in Moravia in 1577. This epidemic in Paris attracted much attention and the term acrodynia was coined for the disease. Recent experience with palmar and plantar skin lesions in pellagra has led me to suspect that acrodynia is a type of pellagra. The diagnosis of acrodynia had to be withdrawn because of the subsequent development in the patient of the typical skin lesions of pellagra. If this is a correct observation and the French were correct in identifying acrodynia with the outbreak at Brünn it may be possible to trace the history of pellagra back to this period. It seems very probable that the disease occurred in Europe in the sixteenth century at least and probably much earlier.

In 1864 the first case of pellagra in the United States was reported by Gray, in Utica, N. Y., and Tyler, in Somerville, Mass. It was claimed that an epidemic occurred in the seventies in an insane institution in South Carolina. Two cases were reported by Pope in a South Carolina penitentiary in the eighties. Numerous sporadic cases, usually imported, were reported from time to time until 1907 when Searcy, in Alabama, recorded an outbreak in an insane institution for negroes. In this outbreak there were 88 cases with 57 deaths. This attracted wide attention in the southern states and resulted in the immediate recognition of the disease in six states. Much difficulty was experienced in making the diagnosis at that time because of the acute fulminating type assumed by the disease as the Italian accounts failed to mention such a condition. In many of the early cases the whole course occurred in six weeks and the classical chronic features were not present, although the skin, mouth and intestinal symptoms occurred in typical form.

From 1907 until 1915 pellagra was very prevalent in the United States. In the earlier years of this period many states had thousands of cases with a high death-rate. During the past decade the disease has gradually decreased until now in many states it is a rarity. Italy for many years has been regarded as the home of pellagra, in part due to the contributions made by Italian observers. In 1879 the number of cases was 97,855; in 1881, 104,067; in 1899, 72,603; in 1905, 55,029. After Italy, Roumania suffered most from pellagra. In 1901 there were 33,645 cases; in 1905, 54,689 cases; in 1906, over 100,000 cases.

Chief among the other countries suffering from pellagra were Austria, southern Russia, Greece, Poland, Servia and Bulgaria. Numerous cases have been reported from the West Indies, Egypt, Asia Minor, India, the Philippines, Mexico and Central America. There are far more cases in Great Britain than formerly suspected. Sambon collected 180 cases and there have been a number of further observations.

Etiology. The cause of pellagra is still regarded as unknown by the majority of observers. One who has followed the developments in its study during the last twenty years cannot fail to be reminded forcibly of the story of the final solution of the beriberi problem. In the two there are many parallels. Since the first account by Casal there have been numerous observers to claim that faulty food was the prime factor and for many years in Italy maize was regarded as the direct cause. This belief was so firmly fixed that when a case occurred in which a history of corn consumption was lacking the diagnosis was made of pseudo-pellagra. Lombroso gave form to the maize theory. He believed the disease was caused by certain moulds, as the *Penicilium glaucum* and the *Aspergillus fumigatus*, which in themselves were not toxic but which by their action on the maize produced certain highly toxic products. The germ of maize lies at the hilus of the grain and is quite soft as well as poorly covered. When the grain is damaged by animal pests, as rodents, or by vegetable pests, as moulds, it is this portion which suffers. This germ contains practically all of the essential food factors (vitamines), water-soluble B and fat-soluble A. It has been suggested that Lombroso's toxicity may have been deficiency and that if the one word had been substituted for the other his contributions would have been the final word in the matter of the etiology of pellagra.

Study of the modern milling of maize tends to strengthen this theory. Formerly maize was ground *in toto* but because of the rapid development of rancidity the practice of degermination was introduced. By this method the germ is removed and the endosperm alone is ground into meal which can be exported because of its good keeping qualities. The percentage of phosphorus pentoxide in the germ and bran of maize is 1.5 while that of maize ground *in toto* is 0.78 and that of highly milled maize without germ is 0.29. During the years of the great prevalence of pellagra in the southern states I observed that there seemed to be a definite relation between the abandonment of the old water grist mill and the introduction of modern milled corn meal. In the one the grain had been ground *in toto* with nothing removed, while in the other all the germ and the bran were removed with the result that the modern product was extremely poor in the essential food factors. Another evil of the same sort was the use of "self-rising flour." This product consists of highly milled wheat flour to which is added a baking powder consisting of acid sodium phosphate and bicarbonate of soda. The baking powder is so adjusted as to give a slightly alkaline end-product. It has been suggested that there is enough of the alkaline end-result to be harmful to the already deficient amount of essential substance. Voegtlin pointed out the harmfulness of the addition of soda in the cooking of vegetables and also of the cooking of food in fat. In many of the cotton mill villages in pellagrous

areas the practices existed of cooking vegetables with fat pork, adding soda to the vegetables to hasten the cooking and the use of highly milled wheat flour and chemical rising agents. These practices with an insufficient protein element have been strongly suspected as playing the chief, if not the sole, part in the causation of many cases.

Goldberger's contribution to the etiology of pellagra seems to many students of the disease to be conclusive while others do not accept it. The three points on which his claims are based are (*a*) that pellagra is essentially of food origin, (*b*) that pellagra never develops in those who eat a well-balanced and varied diet, and (*c*) that the disease depends on an error of diet in which there is a disproportionately high vegetable and cereal element and a low animal or leguminous protein component. In an orphanage with many cases of pellagra it was found that children of a certain age invariably escaped. Investigation revealed that the children escaping the disease were those receiving milk; with a corrective diet, in place of the 75 per cent. incidence, during the next year there was not a single case among 234 children. A selected diet which was thought to be capable of producing the disease was given to a group of volunteers in a pellagrous district but removed from contact with pellagrins and all other claimed sources of infection. The only source of hygienic error in this experiment was an unbalanced diet high in cereals and vegetables and low in protein. From this feeding-test a disease condition resulted which Goldberger and other regarded as pellagra. One of the chief objections to the acceptance of these findings was the atypical location of the skin lesion on the scrotum. Another objection was that the experiment was conducted in a region where pellagra was endemic.

To another group Goldberger administered the feces of pellagrins. No pellagrous symptoms resulted. This was criticized because the subjects were healthy people without preëxisting diseases. It has been generally recognized that such conditions as uncinariasis and dysentery play a large predisposing part in the production of pellagra.

In several hundred cases I have carefully investigated the actual diet of the patient and almost invariably found that the faults pointed out by Goldberger existed. An occasional case among the well-to-do called for particular attention with the result that the victim invariably was found to be either a food crank or one with a vicarious appetite, eating only a single article of food. One among these latter was a young woman who ate only biscuit and coffee. Her symptoms disappeared on a correction of diet. Among many aged people, appetite is lacking and it was found that a considerable percentage of my series was aged unmarried men who lived on small farms alone and having no stimulus of a normal appetite did as little in the way of preparation of food as possible. The diet in such cases was usually canned food with "crackers" or biscuits. The biscuit was made of highly milled wheat flour. These people never drank milk nor ate any dairy product. It was soon obvious that pellagra did not occur among those who regularly drank milk in any reasonable amount. The drinking of milk was found to be an off-set for many gross faults of diet.

In 1912 P. A. Nightingale, in Rhodesia, reported an outbreak of pellagra

in a jail. The prisoners had always been fed on a form of maize known as rapoko which was ground *in toto* in the jail by the prisoners. At the time of this observation the crop had failed and the authorities were forced to buy mealie meal which corresponds to the commercial corn meal of this country. Following this change of diet a severe type of pellagra appeared. A change of diet wrought a result reported as "immediate and magical." Impressed with the results of Nightingale's work, I fed pigeons on corn meal deprived of the germ according to the modern milling method and produced polyneuritis gallinarum with lesser degrees of the same condition representing various degrees of deficiency. The results were in accord with the work done with polished rice and rice polish. Applying these results to the treatment of pellagra it was found that the feeding of the patient with the germ caused improvement which

FIG. 96

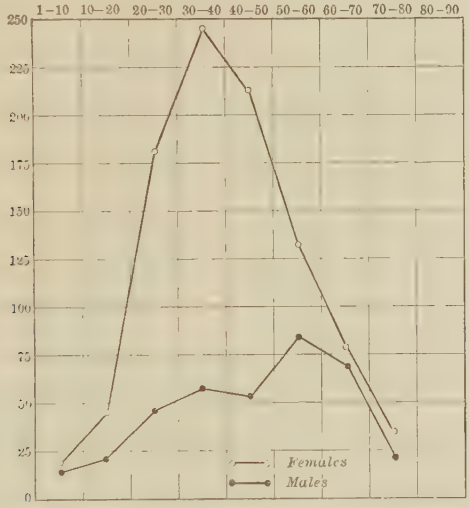


Chart showing relative mortality of pellagra in males and females. Horizontal figures, ages by decades; vertical figures, number of deaths. (Compiled from statistics of Texas State Board of Health for years 1907–1912.)

was immediate. This observation suggests that the deficiency in pellagra is in the water-soluble B factor or that it occurs with this factor in the grain and is removed with the water-soluble B in faulty milling processes.

F. B. Boyd and his associates of the British Army studying pellagra among Turkish prisoners of war in Egypt concluded that the amount of labor done by the victim had a large part to play in the precipitation of symptoms. An individual at rest might escape visible manifestations of the disease while the same individual at work would manifest symptoms. The failure of utilization of protein in such conditions as dysentery or helminthic infestations was found also to play a determining part. It was thought that the loss of essential protein constituents was important because of the possibility of converting an adequate protein diet for normal individuals into an inadequate one for pellagrins.

Jobling and Peterson after an epidemiological study of pellagra in Tennessee concluded that it was an infection the exact nature of which was not known.

The Thompson-McFadden Pellagra Commission contributed much important data to the etiology. The field work of this commission was done in South Carolina. The conclusions were: (*a*) That the eating of sound or diseased maize played no part in the disease; (*b*) that the disease in all probability is a specific infection communicated from person to person by unknown means; (*c*) that there was no evidence connecting the transmission of the disease by insects as intermediaries, and (*d*) that intimate association in the household and the contamination of food with human excreta were suggested as possible modes of transmission.

Goldberger made an important announcement regarding an essential food factor in pellagra. His conclusions are as follows: "(*a*) A liberal supply of protein presumably of good biological value does not completely prevent, though it may modify, the clinical picture of pellagra by notably delaying or preventing the development of the distinctive dermatitis. This modifying action may be of an indirect, sparing nature. (*b*) In the prevention (and presumably causation) of pellagra there is concerned a heretofore unrecognized or unappreciated dietary factor which we designate as factor *P–P*. This may be effective with but little, possibly without any, coöperation from the protein factor. (*c*) Factor *P–P* may possibly play the whole essential role in the prevention (and causation) of pellagra. (*d*) Factor *P–P* is present in brewer's yeast, in milk and (on the basis of our experience with fresh meat) in lean beef; it is very low or lacking in dry soy beans, fresh cowpeas, butter, cod-liver oil and canned tomatoes."

Pathology.—The pathological changes are chiefly in the skin, the intestinal tract and the nervous system. Various changes in the different organs have been observed and recorded but are in no way distinctive and are common to many other debilitating conditions.

The *skin lesion* has generally been regarded clinically as an erythema but a more exact classification must make it a dermatitis except in the very earliest stage. Usually the division into a dry or exfoliative and a wet or exudative form is made. In the former the erythema is either followed promptly by exfoliation or it may pass into a true dermatitis. In the exudative type there occurs the formation of blebs and bullæ, which may become hemorrhagic, though this is rare. The bullous lesion is followed by a weeping condition, resulting in crust formation. In this type secondary pus formation frequently occurs, which complicates the situation and may result in more extensive skin damage. Merk regards this type of lesion as similar to the erythema exudativum of Hebra. In most accounts hyperkeratosis is given a prominent place. Hartzell found hyperkeratosis, perivascular collections of round cells in the corium with œdema of the collagen fibres. Sequira described infiltration of the dermis, especially the papillary layer, with œdema of the connective tissue, parakeratosis of the stratum corneum and infiltration of the rete Malpighii. Most of the writers emphasize the atrophy which occurs universally at the termination of the process and which is one of the dis-

tinctive features. *Pigmentation*, a distinctive feature, is especially marked in the vast majority of skin lesions. It affects the superficial layers of the skin and extends slightly beyond the outer border of the active disease area so that usually for months after the subsidence of any other sign this pigmented border persists. This was originally described by Merk and is known as Merk's hyperkeratotic border or line.

Early in the course of pellagra the whole buccal mucous membrane is the seat of an acute diffuse inflammation which involves the tongue, the gingival surfaces, the buccal surfaces and extends throughout the pharynx and even into the œsophagus. Ulcerated areas soon appear which are found chiefly along the tongue margins, beneath the tongue and on the buccal surfaces, especially opposite the last teeth. Denudation of the tongue follows the inflammatory process and repeated attacks produce a characteristic atrophic appearance.

The changes in the stomach are variable and indefinite. Hyperemia is often recorded but is not of the importance of the congestion found in the duodenum and jejunum with consequent atrophy of the submucosa. Ulceration of the jejunum and ileum have occurred and death from hemorrhage has resulted in my experience. Muscular atrophy occurs and the final appearance of the bowel is that of marked attenuation. Hyperemia and ulceration of the rectum are often noted and Marie mentions chronic enteritis with or without cicatricial constriction, thickening of Peyer's patches and cystic degeneration of the submucous glands.

Fatty infiltration, brown atrophy and fibrosis have been found affecting the myocardium but in many cases these changes have occurred in the presence of other complicating diseases or in the aged. There are no distinctive changes in the liver. Cirrhosis has been reported and also fatty changes but these are in no way distinctive nor has it been shown that some coexisting cause was not responsible. Some writers state that the kidney is seldom if ever normal. The sclerosis and fatty changes found cannot be regarded as distinctive of pellagra.

The most distinctive changes in pellagra are found in the *nervous system*, especially in the spinal cord. The work of S. A. K. Wilson has added much to the knowledge of these changes. He found the areas of degeneration pseudo-systemized mainly in the posterior and lateral tracts, resembling a combined sclerosis but never confined to the limit of any tract. The process should never be regarded, therefore, as a systematized tract degeneration. Marginal degeneration is a prominent feature and degenerated fibres can be found throughout the whole of the section. Wilson found the changes in the nervous tissue to resemble strikingly those of subacute combined degeneration and based this opinion largely on the occurrence of myelin degeneration of a diffuse sort, the presence of compound granular corpuscles and an absence of inflammatory reaction around the bloodvessels. It has been repeatedly observed that Clarke's column seldom escapes some damage. Perinuclear chromatolysis, displacement of the nucleus, swelling of the contour of the cell with pigmentary degeneration and atrophy have been observed by Wilson and others. Wilson also found marked changes in the peripheral nerves. Ehrlich's mast cell is interpreted as an indicator of reaction to toxic

invasion. Spiller found intense degeneration of the cells of the anterior horns in the lumbar region. The cell bodies were swollen and the nuclei displaced to the periphery with the disappearance of many dendritic processes. He concluded that pellagra did not produce a true system degeneration and that the process was caused by some toxin affecting all parts of the cerebrospinal system with cellular degeneration and diffuse alteration of the nerve fibres, especially in the posterior and antero-lateral tracts.

The ganglion cells in the posterior roots have shown subacute inflammatory changes. Babes and Sion noted the occasional occurrence of degeneration of the posterior roots. Tuczek found changes in the central canal of the cord similar to syringomyelia. H. A. Cotton found a marked similarity to central neuritis chiefly indicated by the axonal reaction in the large motor cells and in cells in other regions. The whole process is regarded as a parenchymatous degeneration of the central nervous system. Many observers have found involvement of the pia mater. Sometimes there is a thickening with purulent exudate or hemorrhagic extravasation. Inflammatory changes in the arachnoid were found by Liberali. Verga found hydrops of the ventricles and softening of the cerebral substance. Bianchi recorded thickening and adhesions of the meninges, atrophy and induration of the cerebral substance, increase in the subarachnoid fluid, profound alteration of the cerebral cells and increase in neuroglia.

Incidence.—Pellagra has been reported in infants as early as the third month by the French. My youngest case was aged one year. Many cases occur in the eighth decade. In my series the highest incidence was 28 per cent. in the fourth decade, followed by 24 per cent. in the third decade. In Merk's series the highest incidence was in the fifth decade with the fourth following. Statistics generally have tended to show a comparative infrequence of pellagra among children. As a rule these published returns are too low and this is explained by the mildness of the disease during the first decade. Many cases occur with no other symptom except the symmetrical erythema and never receive medical attention. This fact was learned in routine inspection.

Writers have differed greatly in statements regarding the relation of sex but it is now generally recognized that females suffer more than males. In North Carolina, in 1911, there were 176 deaths from pellagra. Of this number 95 were in females and 81 in males. Since that time the relative increase in the number of cases in women has been notable. Of these 176 deaths, 63 were in negroes. Several factors make this misleading for the incidence is far greater among the whites than would be inferred from this data. The smaller incidence among the negroes is a matter of some importance in a study of etiology.

The relation of *occupation* to pellagra incidence has been carefully studied in the epidemiological surveys. The disease is strikingly a rural one, occurring chiefly in the farming and in the cotton mill classes.

The *geographical distribution* of pellagra in Italy has been curiously reproduced in North Carolina. In Italy it was always regarded essentially as a sub-Alpine disease occurring in the foot hills. In North Carolina the Piedmont section has been attacked much more than the high

mountainous section or than the coastal plain. I have however, found many cases within sight of the Atlantic Ocean and a few cases have occurred in the high mountains. The population is much more dense in the Piedmont section which must be brought into consideration. It is in this section that the greater number of cotton mills is found and the cultivation of cotton and tobacco reaches the highest point.

Symptoms.—The only manifestation of pellagra may be an insignificant skin lesion on the backs of the hands or the neck or in children on the legs. This, however, is exceptional except in the occurrence in children. In the vast majority of cases there is a prodrome which usually begins late in the winter and may not be followed by any definite symptom for many months. In some cases there occurs every year for several seasons a group of indefinite symptoms which must be regarded as representing pellagra in the light of subsequent events. The complaints during this period are many and varied. Usually there are indefinite and ill-defined digestive symptoms which cannot be attributed to any organic change. Depression is common and vertigo is usually present and may persist throughout the whole course.

The order of the appearance of symptoms and signs is variable. The triad of stomatitis, diarrhœa and symmetrical skin lesions usually occurs. In some cases diarrhœa is lacking and there may be stubborn constipation. In a smaller group stomatitis is not observed. In many cases the stomatitis is so slight that there is no complaint and it is so inconspicuous that it escapes casual observation. The question of the necessity of the skin lesion for a diagnosis is still debated. It would seem wisest to regard the skin lesion as the pathognomonic sign and to withhold the diagnosis in its absence unless the history of previous outbreaks can be obtained. By doing this a few cases may be overlooked but, on the other hand, many errors of a more serious nature will be avoided. In doubtful cases without skin lesions exposure to the direct rays of the sun will usually decide the question. Many doubtful cases can be settled by an examination of the whole skin surface. Perianal, scrotal and perivaginal lesions may be detected which are just as much a part of the disease picture as the more generally recognized lesions of the extremities and the neck.

Diarrhœa and sore mouth may precede the appearance of the skin lesion by weeks or months and in some cases by one or more seasons. In some cases the mouth changes appear first while in others the order is reversed. In many instances the appearance of the two is simultaneous.

The relation of the onset of pellagra to the seasons is an important characteristic. The prodromal symptoms are noted usually late in the winter and the sore mouth and diarrhœa follow in the early spring, frequently just before the beginning of warm weather. The skin lesion appears with the early summer and seems to be influenced by the character of the season. If hot weather occurs early the skin lesion usually is also early, while in the years of delayed summer weather the skin lesions will be retarded. In this is seen something of the importance of the part played by the sun in the causation of the skin manifestations but there is some other determining factor as is proved by the appearance of the lesion in bed patients on the feet, the back and about the genitalia. These

lesions preserve the same exact symmetry which is seen on the uncovered portions. In a small proportion of cases the initial symptoms first appear in the autumn. When the initial appearance is in the spring a second appearance in the autumn is not infrequent. In a series of about 2000 cases I saw no winter appearances. The initial appearance of a skin lesion in the winter months is a reasonable basis for the exclusion of pellagra.

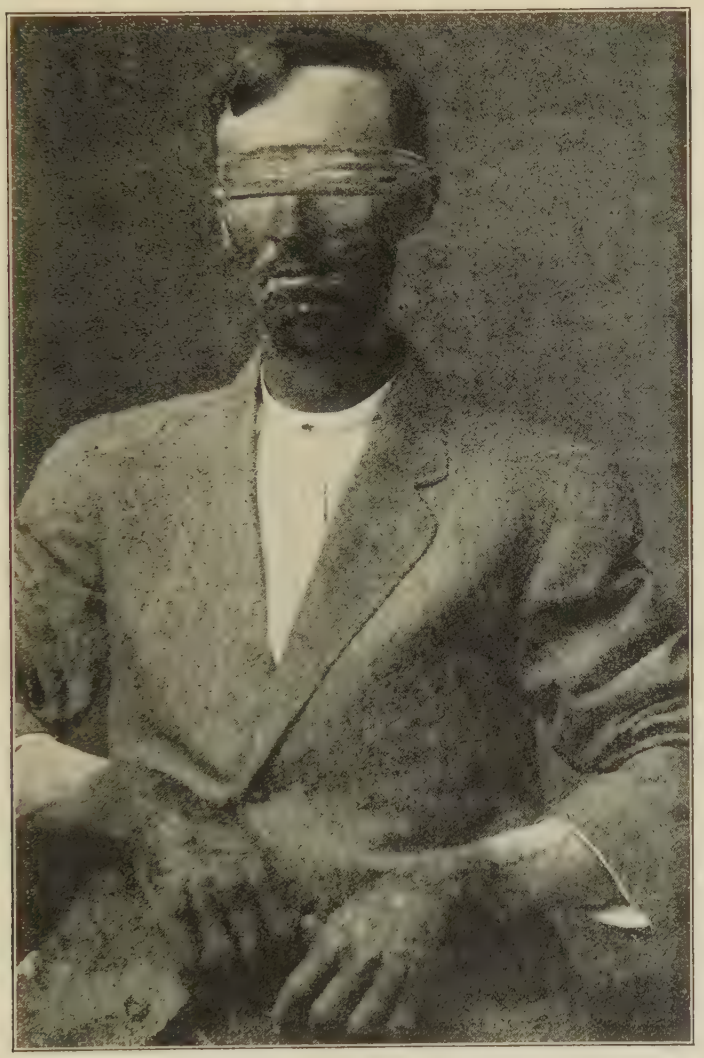
There are many variations in the degree and severity of the *stomatitis*. It may be so trifling that no complaint is made and it is entirely overlooked, or it may be so severe that it overshadows the other symptoms. In many cases the suffering from it is great. In the severe type the mucous membrane of the whole mouth cavity is intensely inflamed. The color of the tongue and mucous membrane is a deep red and much like that of scarlet fever. The tongue is usually firm and pointed with red edges, if not red throughout, and may be encircled with aphthous ulcers. These ulcers may also occur on the inferior surface especially about the frenum and occasionally on the superior surface. Salivation is seldom absent and may vary from a slight increase to a constant trickle of saliva. The salivary glands may be swollen and sensitive to pressure. The fungiform papillæ are enlarged and stand out prominently until several attacks of glossitis causes complete denudation, leaving the tongue bald and smooth. Sandwith called it the "beet tongue" because of the intense redness at the height of the process. The duration of mouth symptoms is variable but as a rule subsidence occurs before the termination of the diarrhœa. Patients first seen on account of the skin lesion may present no mouth symptoms but a very definite history of them.

Diarrhœa was present in 77 per cent. of the cases of my series. It varied in degree as much as did the mouth symptoms. In some cases it presented a grave problem. The movements occur at all hours without the matitudinal tendency of sprue. The stool is liquid and lacks any distinguishing feature. Study of the feces after test diets demonstrates a normal utilization of both fat and protein. Pain and tenesmus may be distressing and resist all of the usual measures of relief. Diarrhœa may persist for months after all other indications have disappeared just as it may have occurred for several seasons before the full disease picture was noted.

The *skin lesion* is one of the most distinctive and clear-cut pictures in medicine. The outstanding feature is the perfect bilateral symmetry, which includes the size, shape and location of the lesion. The pattern of the one side is perfectly reproduced on the other and can be anticipated with certainty when the lesion on one side precedes the other. On this symmetry alone the diagnosis can usually be made. There is usually a sharp line of demarcation at the border of the skin lesion. *Pigmentation*, which usually is a distinctive feature of the skin lesion, is emphasized at or near the border of the affected area. Healing proceeds from the centre to the periphery and just within the free border will be found a line of deeper pigmentation which persists long after the process has run its course and subsided. This is the hyperkeratotic border of Merk and on it alone the diagnosis has often been made when no other evidence

of skin lesion was present. Pigmentation is mentioned in all accounts of the skin lesion of pellagra. It is a variable quantity and its lack has caused some confusion. In fair people it is less than in the brunette types. It is most conspicuous in the Egyptian and in the mulatto. In the negro

Fig. 97



Pellagra in an adult, showing the pellagrous erythema.

it is inconspicuous only because of the contrast. The intensity of the sun's rays plays a determining part in its development. In Great Britain pigmentation is not so marked as in southern Europe or in the southern states. In 1 case observed in Edinburgh which was otherwise typical and in which the diagnosis could not be questioned there was no apparent

pigment increase. In the dry type of skin lesion pigmentation is especially pronounced and frequently before exfoliation the whole affected skin area assumes a brown or mahogany color. In the bullous type there is not so much opportunity for the study of pigment changes because of the nature of the disease process. The action of the sun's rays in the final appearance of the skin lesion is of great importance as exposure to the direct rays of the sun frequently settles a doubtful diagnosis. The commonest mistake in the diagnosis of the skin lesion is confusion with sunburn, which it closely resembles. It has been repeatedly noted that fenestrations in the clothing will determine the distribution of the

Fig. 98

Showing symmetrical erythema extending up the forearm.

erythema. In one of my cases in which the skin of the back was affected the only part which escaped was that covered by the shoulder straps of the underclothes. In children going barefooted the skin lesion occurs on the legs and feet as frequently as it does in adults on the backs of the hands. The lesion may be found on any portion of the skin surface regardless of clothing.

The most frequent *location* of the pellagrous skin lesion is the backs of the hands. This location was the one affected in 97 per cent. of this series. The extent may be so slight as to amount to little more than a chapping of the knuckles or the whole posterior surface of the hand may be involved. Sometimes only a small area in the metacarpal region is

affected. Occasionally the posterior surfaces of all the fingers are included. I have never seen the lesion affect the finger nails in any way. Frequently the lesion involves the whole of the posterior surface of the forearm and such cases made up 10 per cent. of the series. In 5 per cent. the forearms only were affected. In 39 per cent. of the cases the backs of the hands alone were affected. In 16 per cent. the feet were affected but always in combination with other parts. In 8 per cent. the face was affected but this seldom occurred alone. The face lesion varied from a small

FIG. 99

Child of four years with lesions on head and neck, arms and hands, penis, knees and feet.

patch on the forehead to an involvement of the whole skin surface, the so-called pellagrous mask. Often there were tiny areas at the outer canthi of the eyes. In some cases there was a lesion encircling the eye with a tendency for it to become hemorrhagic and to simulate a "black eye." On one occasion a patient had such a black eye supposedly due to the patient having fallen out of bed. A repetition of the "accident" was predicted and it occurred a few days later fulfilling the law of symmetry in all pellagrous skin lesions. Trauma and accidental agencies have played a prominent part in the earlier history of pellagra in this country.

In one insane institution attendants were discharged for allowing patients to be burned in too hot baths. Later the supposed burn was found to be the skin lesion of pellagra.

The location of the lesion on the neck is very frequent; it was noted by Casal in the first authentic account of the disease and is called "Casal's collar." The lesion frequently encircles the neck completely. In some cases an extension downward over the sternum and in others downward along the spine occurs. In adults especially it should be sought for and frequently along the upper border of the neck line Merk's hyperkeratotic line will be found after the subsidence of the process.

In 6 per cent. of my series covered portions of the skin surface were affected but in no instance was this the only portion involved. Since the study of this series this number has increased because of a more careful routine search for the lesion. In one case the scrotum was the first portion affected but later lesions in the more expected locations occurred. Lesions in and about the vagina are much more frequently recorded since the institution of routine search for them.

Lesions of the palmar and plantar surfaces are by no means frequent. In my experience both have occurred. In one case the diagnosis of acrodynia was made on account of this distribution but later the diagnosis had to be revised because of the appearance of the lesion in more typical locations. There is no portion of the skin surface which has escaped the lesion of pellagra.

Occasionally a skin lesion occurs with a peculiar lamellated appearance suggesting the layers of an oyster or clam shell. The presumption is that the first lesion was the most extensive and the next occurred before the first had healed and was not so extensive. Each subsequent exacerbation was less in extent until the last was hardly more than a mere point. This is seen chiefly on the upper arm and while infrequent it is quite distinctive.

After exfoliation the skin is found to be soft and velvety and is really thinned out and atrophic. Many recurrences in the same location add to the atrophic condition.

Neurological manifestations occur in the vast majority of cases. The exceptions are chiefly in little children who usually escape any nervous involvement. In early stages vague and indefinite complaints suggesting a functional nervous disturbance are frequent. Study of the reflexes and of sensation at this time usually reveals nothing. Throughout the whole process mental depression occurs. When the patient with marked features comes to observation the tendon reflexes in a majority of instances are exaggerated and in a smaller number they show a marked decrease even to complete absence. The tendon reflexes on one side may be exaggerated and on the other side decreased or absent; early in the process the reflex responses vary from time to time. Probably the most frequent finding is one identical with or closely resembling subscute combined degeneration. This is manifested by sensory disturbances, spasticity of the limbs and weakness of the sphincters which later may amount to complete loss of control. The plantar reflex is extensor in type (Babinski's sign). The spastic paraplegia may give way later to flaccidity with loss of all reflexes. Soon after the appearance of the nervous symp-

toms coarse tremors frequently occur which may be confined to the extremities but may also include the head. These are sometimes described as athetoid, and clonic convulsive movements have been noted to alternate with tonic spasms lasting a short time with a period of relaxation and then a repetition of the clonic movement. Muscle spasms and cramps have been recorded. Epileptiform seizures have been observed and one such case has come under my observation. Another case, a negress, aged seventeen years, died suddenly with circulatory symptoms strongly suggesting the Stokes-Adams syndrome. Neusser described a case of amyotrophic lateral sclerosis in pellagra and the inference was that there was an etiological connection. One of my patients presented the typical picture of Landry's paralysis and died from respiratory failure. Peripheral multiple neuritis occurs and one such case was studied in the service of Edwin Bramwell in the Royal Infirmary, Edinburgh. The gait in pellagra is unsteady and otherwise varies greatly, depending on the lesion. Anderson has called it a "spraddle legged gait."

The *mental manifestations* may occur at the onset, be delayed for months or, in some cases, even for years. One patient presented marked mental changes resulting in his confinement for months before the diagnostic evidence of pellagra appeared. The predominating feature throughout is mental depression in varying degree. At the start there may be restlessness which increases in many cases far into the attack. It is common to see a pellagrin at the height of the attack lying in bed but keeping the body in constant movement. Restraint is often necessary.

Gregor divided the mental manifestations into seven groups. The mildest, called the neurasthenic group, was characterized by restlessness and depression. The second was an exaggeration of the first group in which there was mental apathy but normal orientation. Replies to questions were much delayed. In the third group there was mental aberration with depressing hallucinations and violent motor excitement. In this group came the cases marked by somnolence and muttering delirium and also of profound dementia. Katatonic symptoms were also recorded. The next group was merely an exaggeration of the third, to which was added acute delirium, a feature of the disease usually followed by early death. In the fifth group fell most of the cases of katatonia, "a condition of excitement with stereotyped actions, wild jactitation and verbigeration" with a rapid transition into dementia. The sixth group include the cases of anxiety psychosis in which a sense of insufficiency is usually noted and there are indications of mild stupor. The seventh group included the manic-depressive cases which were attributable to pellagra. Many cases fail to fit into any of these divisions in spite of the flexibility of the classification. In no instance was a case noted with symptoms of exaltation or delusions of grandeur. There is always profound mental depression with delusions of persecution and religious doubts and fears, especially of the unpardonable sin.

In North Carolina it was estimated that 40 per cent. of the patients became mentally disturbed to such a degree that institutional treatment was necessary. In recent years the decreasing number of cases of pellagra shows decreased severity and these milder cases have been recognized

earlier, permitting hygienic corrections at a time when something could be accomplished. The decrease in the number of serious mental complications is notable.

Diagnosis.—In the presence of the three great features, skin lesions, diarrhœa and stomatitis there can be no occasion for confusion or even for any differentiation. In the presence of the symmetrical skin lesions the diagnosis should be made without hesitation, and if the lesion has healed the hyperkeratotic border of Merk makes recognition easy. The possibility of confusion with syphilis has been suggested. Even without the Wassermann test there is no real occasion for difficulty. The skin lesion does not simulate any of the types of syphilis, the mouth symptoms are entirely different and the diarrhœa is suggestive, especially when it occurs with the other features. The late neurological and mental manifestations when the skin lesion has disappeared offer more possibilities of difficulty but a spinal puncture and study of the fluid removes all doubt. *Pellagra-sine-pellagra*, or pellagra without skin lesions, offers a problem of great difficulty. In the light of recent advance in treatment from the nutritional point of view, early diagnosis is greatly to be desired. When mouth and intestinal symptoms occur and a definite error in diet is found the suspicion of pellagra is justified and a correction of diet is in order even if pellagra is not present. Such a diagnosis in the absence of any exact laboratory tests must be uncertain but in the light of Goldberger's contributions more effort should be made to keep such a possibility in mind. Pellagra-sine-pellagra has been confused with sprue but the points of difference are sufficient to settle most cases. The difference in the character of the diarrhœa, in the mouth symptoms and the blood changes in sprue, which do not occur in pellagra, can be readily determined. Formerly it was thought that neurological changes did not occur in sprue but subacute combined degeneration of the cord may occur, a condition met with in grave pellagra. The seasonal variation of pellagra is helpful.

Prognosis.—This varies under many different conditions. Five of 6 cases reported by me in 1909 died. In one house there were 3 deaths after a duration of not more than six weeks in any case. In the early years of our American experience with pellagra the condition was unique, for it was acute pellagra while all accounts in the literature were of a chronic condition. At that time the death-rate frequently reached 80 per cent. and many of the deaths occurred during the initial outbreak. The disease has gradually lost its acute characteristics and has now reached the usual form described in European literature. In recent years there has been such a remarkable decrease in incidence that in the territory in North Carolina where my observations have been made it is now a rarity. The few cases are eagerly studied and there is no delay in applying hygienic remedies long before structural neurological change occurs. The outlook in such cases is entirely different from what it once was in Europe. Some authorities regard pellagra as an incurable disease but there are many American patients entirely well today who had pellagra fifteen or twenty years ago. In Europe the peasant in the pellagra districts might remain free from the disease if he did not resume the living conditions responsible for pellagra. In America there is no occasion

for death from pellagra if the diagnosis is made reasonably early and the patient follows instructions. Some years ago Lavinder estimated the American death-rate to be about 25 per cent. and the asylum death-rate to be 67 per cent. Lombroso in 1884 reported the Italian death-rate to be 13 per cent. and Sambon, who regarded the disease as incurable, reported a death-rate of 4 per cent. The prognosis from the mental point of view is an important problem about which the data are still insufficient. Many mental patients with pellagra recover after the pellagra begins to subside but it must be kept in mind that the patient was gravely affected if mental manifestations occurred even in mild form. Certainly the outlook for the patient without mental symptoms is much brighter and the absence of cord changes likewise is favorable. The outlook when subacute combined degeneration of the cord occurs is as grave as if the lesion was due to another disease.

Treatment.—The most important element is a prompt diagnosis. A careful investigation of the patient's dietary should be made, remembering that it is not what is on the table but what is actually eaten with which one must be concerned. In recent years I have not failed to find gross defects in every case so studied. The error must not only be corrected but overcorrected. Regardless of what the error is the best offset consists in the abundant consumption of milk, eggs and fresh meat, preferably underdone beef. The addition of cream is helpful. The citrus fruits should be eaten freely every day. Raw and cooked leaf vegetables must be included once a day at least. Forced feeding should be tried and if the patient does not coöperate because of the mental state it is well to feed through the tube rather than be content with an insufficient amount of food. A gruel made of the germ of Indian corn or the bran and cortical parts of wheat is useful. This gruel can be strained and milk, cream and eggs added. The patient usually improves enough to be willing to coöperate after a few days of such treatment. Goldberger's work on what he designates the *P–P* factor, obtained for his experimental work from brewer's yeast, has opened a new field in the treatment of pellagra. This brewer's yeast can be had in tablet form and is administered by mouth. It has given encouraging results and is known as Yeast-vitamine (Harris). The results from giving the germ of Indian corn freshly milled have been excellent. Patients who for months have suffered from diarrhœa have been relieved by giving as the sole food a gruel made of this corn product.

Drugs of many kinds have been used but there is no reason for believing that any has done good and it seems probable that some have done harm. Arsenic has been the favorite and in recent years the preparations which can be given hypodermically have found special favor. The disease usually subsides in a comparatively brief time and always with the advent of cold weather. The hypodermic injections of arsenic are too often given the credit for effecting an improvement which is coincident with the seasonal improvement. Some cases of neuritis may have been produced by the large doses of arsenic employed. To give any drug, except possibly something for symptomatic relief, only arouses a sense of false security. If correction of the diet and general hygiene are advocated

alone the patient follows directions much more satisfactorily. Diet is as important as in diabetes and if the patient does not receive this impression nothing but disaster results. The general hygienic conditions under which the patient lives must be investigated and corrected when indicated. Many of these patients improve after a change of scene. Probably too much importance was attached to this a few years ago. Change of scene and climate does good provided it is done with correction of diet. After diet the best single aid is rest and it is almost as important in pellagra as in tuberculosis.

Before the patient is dismissed a general investigation should be made to correct other conditions, such as helminthic infestations and focal infections in teeth, tonsils or accessory sinuses. It is not infrequent to find diabetes and pellagra in the same individual. This problem is made less difficult by insulin. Tuberculosis and pellagra occur together occasionally but this is not such a difficulty as the treatment of one does equally as well for the other. Before discharge the patient should be warned about the likelihood of a recurrence and instructed to make every effort to prevent danger by the best possible dietetic régime. In certain patients, at the anniversary, in spite of proper dietetic precautions a slight symmetrical erythema occurs without other sign or symptom. This is of no consequence and should cause no uneasiness.

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CHAPTER XXVI

BERIBERI

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AND

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Introduction.— Of the problems of "medicine in the tropics" (as distinguished from "tropical medicine"), that of neuritis (including beriberi) is one of the most interesting, baffling and important. It is still very far from being solved. The frequent absence of sharply defined clinical pictures corresponding to types of neuritis of different etiology is a confusing factor in the study of the group and makes the setting up of clinical entities impossible. How many and what etiological entities are included in the clinical term tropical neuritis has not been sufficiently studied by modern methods. Until this has been done, beriberi must remain a clinical diagnosis of widely diversified meaning. Much of the confusion in medical literature about tropical neuritis and beriberi has arisen because many investigators have included neuritis of more than one etiology in their discussion of beriberi.

All factors recognized as causative of neuritis elsewhere are active in the tropics, and there are probably other factors limited to warm climates. Among the agencies of particular interest to the student of neuritis, including beriberi, in the tropics are the following:

Conditions inherent in the patient, including hereditary influences and possibly intra-uterine diseases, cannot be ignored as predisposing factors in at least certain classes of neuritis.

The report of the government committees for the investigation of infant mortality in the Philippine Islands records an average intra-uterine death-rate of over 30 per cent. The causes of these deaths are in part at least unknown, and a predisposing influence to disease of the nervous system among those who do not die is generally recognized. "Taon," or infantile beriberi, takes a frightful toll in some beriberi zones and many are convinced that this mortality extends to prenatal life. The anatomical, physiological and social status resulting from poor heredity, acquired disease and widespread malnutrition might well be supposed to leave the nervous system particularly susceptible to neuritis.

It is probable that *physical agents* are more important factors in the production of neuritis in the tropics than elsewhere. This may be due in part to the peculiarities of environment calculated to encourage the development of neuritis. Neuritis of the lower extremities, for example, is unusually frequent during the latter months of pregnancy in beriberi zones, and in many instances the complication may be beriberi, but in

others it has little resemblance to that disease. In this same category must be placed the neuritis from pressure by tumors, aneurism and tight bands worn by certain tropical people which is noted occasionally, and also that sometimes following extensive traumatic wounds. Posture has been thought to be a factor in the preponderating prevalence of neuritis of the lower extremities over that of other parts of the body. Most Orientals rest in the squatting position and they may remain comfortable in such position for hours at a time.

Sudden changes from the lowlands to the cool high-altitude stations and sudden changes in climatic conditions are associated with the development of neuritis too often to be explained by coincidence.

The tropical environment exerts a powerful and constantly acting adverse influence upon the nervous system of all persons. The particular factor or factors are not fully understood, but it is probable that the heat, moisture, sudden change, trying sanitation, worries and fretting, all acting together, rack the nervous system of the foreigner and the native alike. It may be that these conditions prepare the way so that otherwise innocuous agents may cause neuritis.

The best known variety of *inorganic chemical poisons* of particular importance in the tropics is arsenic, and the careful observer finds neuritis of arsenical origin not infrequently. At one time arsenic was considered to be a cause of beriberi. Lead neuritis is rarely seen.

Alcoholic neuritis is the most prevalent type of neuritis caused by organic chemicals. The oft-repeated statement that tropical people are not important consumers of alcohol is open to serious doubt, because most alcohols consumed by the great mass of Orientals are not taxable and therefore not included in statistics. They are largely home-made preparations which may be particularly active in producing neuritis. In any event, alcoholic neuritis is seen in large clinics among all classes, and in many instances a diagnosis of beriberi has been made.

There is a great unexplained field among the unknown local herbs extensively used as medicine by Orientals. Many trees, flowers, weeds, as well as many fish, insects and minerals, are included in the group of cure-alls, some of which are known to contain active poisons.

Toxins introduced in food or formed in the alimentary canal are suspected of being more important in the tropics than elsewhere and may cause neuritis. The capsulated anaërobic bacteria usually forming part of the tropical intestinal flora offer a promising field for investigation. Food poisoning is exceedingly common and intestinal derangements due to infections and the character of food eaten by the poor, may be important in the etiology of neuritis. Toxins formed as products of disease or from deranged metabolism assume special importance in the tropical problem of neuritis. In addition to such diseases as diabetes and nephritis there are an unusual number of anemias, cachexias, fevers and conditions of unknown cause which are not infrequently forerunners, if not producers, of neuritis.

Animal parasites, such as those causing syphilis, yaws, malaria, trypanosomiasis, amœbiasis and schistosomiasis in particular, acting either directly or through their toxins, are responsible for a certain amount of

neuritis. Other animal parasites, including the various intestinal worms, exert a profound effect upon the nervous system, particularly in children, and it is probable that they at times may be the exciting cause of neuritis.

Bacteria causing tuberculosis, leprosy, pneumonia, typhoid fever, influenza, whooping cough, undulant fever, and gonorrhœa in particular, are recognized as producers of neuritis. The unknown causative agents of certain other diseases, as smallpox and dengue-like fevers, also must be considered among the causes of neuritis. The possible application of some of the newer knowledge about diabetes and nutritional disturbances in general may be expected to clarify our conception of neuritis.

The various forms of neuritis discussed up to this point have a much higher incidence in the tropics than is generally recognized. The tendency to diagnose all of them as beriberi without sufficient investigation is more prevalent than it will be when more is known about this remarkable group of diseases. After a series of cases of neuritis in a tropical community have been studied by all possible means and have been classified as far as possible into groups of known causes, there still remain a large proportion unaccounted for, and these we will consider under the most used name—Beriberi.

Synonyms.—Kakke, asjike, loempe, endemic multiple neuritis, panneuritis endemica and many others.

Definition.—A chronic, or less frequently acute, disease or group of diseases caused in whole or in part by faulty food supply, assimilation or metabolism. It is characterized pathologically by a multiple neuritis selective in type for the pneumogastric, phrenic, anterior tibial and peroneal nerves, but extending to other nerves as well; and expressed clinically by œdema, pain, paresthesias and absence of reflexes, particularly in the lower extremities, palpitation and dilatation of the heart, epigastric distress and absence of fever. It is endemic in most tropical and oriental countries and finds its highest incidence among the poor.

Beriberi is one of three or four diseases which, taken together, always have stood as a barrier against civic, economic and social progress throughout the tropical and oriental world. The history of the disease is well told in Vedder's excellent monograph. It has been known in China, Japan and probably elsewhere almost since the beginning of the Christian era. Practically no oriental, tropical or far-eastern country is ever free from it. It occurs sporadically, endemically and pandemically. Without being infectious, it rises and falls and passes in great waves over vast territories.

Certain races appear to have some natural *immunity* against the disease, and certain of the tropical races seem to be especially susceptible to it. Newcomers into a beriberi zone, whether of foreign or native birth, seem to be less susceptible in certain instances, while in others similar change appears to increase the risk to the immigrants. It is probable, however, that all of these observations may be satisfactorily explained by other forces than predisposition and immunity. One or a number of attacks of the disease does not produce immunity, and it is likely that no such quality exists.

Etiology.—Predisposing Causes.—*Prenatal Influence.*—The frequency of the condition in infants and other facts point to the existence of some

influence of inheritance or prenatal disease, or at least to an influence which particularly affects the mother and child during gestation and the infant after birth.

Physical Condition.—Beriberi finds its highest incidence under certain physiographic conditions, climate and rainfall, and is largely confined within certain geographic limits. Environment favorable to the spread of beriberi is that generally described as the east, the orient or the tropics. This does not necessarily mean climate, heat, geography, rainfall, customs of the people, activities, energies or any other one thing, but a conglomeration of these and many others which moulds all residents to a something in common or destroys them. This environment is the home of beriberi, as it is of so many other diseases. It is common in the entire Malay Archipelago, India, Burma, Ceylon, China, Japan, the Philippine Islands, Dutch Indies, Korea, Siam, New Zealand, Australia, Africa, South Sea Islands, South America and on ships on many seas. In some countries it is limited to certain areas, and outbreaks are recorded in many parts of the world. Beriberi has been reported several times in jails and institutions in the United States, and also from Canada.

Seasonally, beriberi appears to be a wet-weather disease, although Vedder and others consider seasons important only as they influence the varieties of avilable food. In endemic areas it is found at all times of the year, but in most places from which we have reliable statistics it reaches its highest incidence during and just after the rainy season. There are exceptions to this rule, and in some locations variation in rainfall is not sufficient to warrant emphasis on the wet season. In the Philippines the incidence curve is highest toward the end of the rainy season and shortly after it, but the difference is not striking, and some of the past epidemics have continued through more than one season. Other physical conditions which seem to be associated with the prevalence of beriberi are shown in its selection of lowlands and river valleys, the disease being less prevalent in high altitudes and in interior cities.

Social Conditions.—The disease may occur at any age and in both sexes, but it is much more prevalent among young adult males and during early infancy. A first attack is comparatively rare among very old people, and, except the infantile variety, it also is less frequent during childhood. While all races are susceptible, native tropical people are the greatest sufferers, and in given localities certain nationals seem more susceptible than others. Thus Braddon notes that while the native Malayan suffers but little, Chinese immigrants in the Straits Settlements and Malay Archipelago show a high incidence and a high mortality rate. In the Philippine Islands the native Filipinos are the greatest sufferers, the Japanese come next, and the disease is comparatively rare among the Chinese. Individuals of the white races rarely contract the disease, except when inmates of institutions or on ships. The disease is rare in all countries among merchants, artisans, professional men, and in general among members of the social upper strata. It reaches its highest incidence among teamsters, farmers, rice workers and others of the unskilled-labor classes.

Poverty.—Beriberi is a disease of the poor, ignorant and superstitious. The poverty factor of great importance is that of quality and quantity of food supply. Poor people buy and eat almost without question what their local community markets supply, and this varies in volume, nutritional value and balance, always being deficient in proteins and fats.

Public Health Conditions.—Beriberi subjects, regardless of race or residence, belong largely to the class who are mostly residents of the slums of Oriental cities. These are frequently located on low shore land, with dirty, crooked, unpaved alleys for roadways, with inadequate or no water supply, and no appropriate means for handling sewage and garbage. House construction is of the adobe stone without proper foundation or elevation, with dark, damp, poorly ventilated rooms; or, in other localities, the house construction is of bamboo or grass.

Overcrowding is the rule in the slums of all oriental cities. House-sleeping is frequently measured by the number of persons who can lie on the floor; both sexes, children, sick and well, often sleeping together indiscriminately in closed rooms. Not infrequently public buildings, such as barracks, prisons, theaters, and amusement halls, are not much of an improvement on the home conditions. Millions of people live under conditions where there is no such thing as cleanliness, as the more intelligent understand the word, and where good health, as ordinarily defined, is rare. These conditions, with variations to meet local custom, give beriberi its highest incidence and are responsible for the former hypothesis that it was a *place disease.*

Personal Health and Hygiene.—Other diseases are not known to predispose to beriberi. Aside from its prevalence among pregnant and parturient women, it attacks persons otherwise apparently in normal health as frequently as it does weaklings. Acosta-Sison holds that besides beriberi other conditions lead to neuritis in parturient women in the tropics, and thinks the diagnosis of beriberi under such conditions is made too frequently. Various diseases and depressing influences, such as the acute infections, mental exertion, emotion and excesses of all kinds, are considered by Scheube and others as predisposing factors. Chomori *et al.* say that the length of the incubation period, the degree of progress of the symptoms, and the fact that some who are on a certain diet contract the disease while others do not, all depend on the constitution and secondary causes. Among the constitutional causes status lymphaticus is the chief. Among the secondary causes are labor in warm moist climate, unhygienic living, digestive disturbances, various infectious diseases, pregnancy and the puerperium.

Exciting Causes.—The theories concerning the etiology of beriberi are numerous. Each theory has been valuable insofar as it has led to accurate investigation of particular phases of the disease and the conditions surrounding its onset and occurrence. In this way the list of possible causes has been narrowed down to relatively few. Study of the changes produced in the patient by the disease has furnished little that throws light on the true immediate causative factor, although predisposing influences have thus been detected. Rather a study of the external conditions surrounding the patients, and especially a study of the epidemiology, includ-

ing diets, has been fruitful in furnishing encouraging working hypotheses, at least concerning the cause of the disease, its prevention and its treatment. While it is probably true that the exact determining cause of beriberi has not yet been absolutely proved, our present knowledge is sufficient to render some of the theories as to its etiology of more than historic interest. These may be grouped under:

(*a*) *Intoxication:* (1) *Inorganic chemical:* arsenic; carbon dioxide; oxalate.

2. *Organic:* Vegetable, including spoiled rice; ptomains and similar "toxins." Animal poisoning, including fish and other animal food poisons. Infections, including specific bacteria, combinations of bacteria; protozoa, nematodes, and fungi.

(*b*) *Deficiencies in diet* that have been blamed include phosphorus, nitrogen, potassium, proteins, fat and vitamins. Poorly balanced, monotonous and insufficient diet as a cause of beriberi is supported by more carefully controlled experimentation than any other of the many theories. In fact, there can be no longer a doubt that certain deficiencies and irregularities in food intake will surely produce neuritis in animals, fowls and man. *It is not so easy to be certain that the food deficiency neuritis is all there is to the disease or group of diseases called beriberi.*

This grouping indicates that practically all the theories that have been advanced recognize that the disease depends on the nature of ingested material, whether the ingested material be harmful through insufficiency, through intrinsic poisonous properties, or by producing favorable conditions for the development or growth of harmful material in the intestine. Almost all of the champions of the bacterial origin of the disease consider the alimentary tract to be the portal of entry.

Aside from those who have described definite microörganisms as the cause of the disease there are others who believe that bacteria, protozoa or fungi may produce changes in the food before consumption, and those who favor the idea that the food forms a favorable medium for the growth of organisms either before or after ingestion.

Concerning the theories which consider inorganic chemical poisons as etiological factors, it may be said that very little evidence in their favor has been deduced; they do not furnish a satisfactory explanation of the clinical or pathological phenomena, and they have met with no general acceptance. The same may be said of the theory of ichthyotoxismus and lathyrism.

Infectious Theory.—Among workers who favor the infectious theory are first, those who claim to have isolated organisms to which have been assigned an etiological role. The findings have not been confirmed or generally accepted. The second group includes those who, from a study of the epidemiology, symptomatology and pathology of the disease, consider that it is best explained by an infectious theory without indicating any special organism. Their reasoning is largely by analogy with known infectious diseases.

Manson believed that beriberi is caused by the introduction by inhalation or otherwise of a toxin generated by some germ without the body. This germ, he believed, may be carried by man from place to place. He

considered beriberi, therefore, essentially a place disease. Scheube based his reasons for considering beriberi an infectious disease upon its occurrence in strong, well-nourished young persons, its geographic restrictions, its seasonal occurrence, and on his belief that it cannot depend entirely on defective nutrition. Wright emphasized the significance of changes in the stomach and duodenum and maintained that these are the seat of growth of an organism which produces an extracellular diffusible toxin, which in turn produces the lesions and symptoms of the disease. Those theories which ascribed an etiological role to nematode parasites have never been given serious consideration, and a protozoan cause has not been proved.

Diet.—From the earliest time a relation has been noted between diet and beriberi. In the search for the causative factor almost every conceivable relation between diet and the disease has been investigated. Especially has its relation to the consumption of rice occupied an important place in the history. In turn, investigators have considered the chemical constituents of the varieties of rice, the time and degree of its decortication, the time and manner of its curing and preparation for consumption, the way in which it is stored, the length of time it is stored, the changes occurring in it while stored, and the amount eaten.

The theory which now attracts most attention and seems most plausible is that which regards highly polished rice as an exclusive or preponderant article of diet to be deficient in a substance or substances necessary for healthy nutrition. The first step toward the proof of this theory was to establish the fact that the consumption of decorticated rice was followed by beriberi. This has been proved experimentally in man by Fraser and Stanton, and by Strong and Crowell. It has also been shown on larger scales, by Braddon, Vordermann, and by Heiser in Bilibid Prison and in the Culion Leper Colony, where substitution of partly decorticated rice for completely decorticated rice led to the practical disappearance of beriberi.

Animal experimentation has been of great value in advancing our knowledge of this disease, or at least of a neuritis very similar to it. Eijkman in Java noticed the development of polyneuritis gallinarum in fowls fed on decorticated rice, and this was soon confirmed by many others. The similarity between polyneuritis gallinarum and human beriberi was noted, and much fruitless discussion has been waged concerning their identity. It is sufficient to consider the two conditions analogous and apply truths elicited from a study of the fowl disease to man with caution. In this way it has been found possible to further our knowledge concerning the cause, prevention and treatment of the disease. It has been shown that fowls fed on fully decorticated rice develop polyneuritis, whereas those fed on slightly decorticated rice do not. From this the idea arose that a neuritis-preventing principle is present in the husk of the rice. It has been found, expecially in the United States Army Board for the study of tropical diseases as they exist in the Philippines, that extracts of this husk (so-called rice-polishings; in Tagalog, "tiquitiqui") if given with decorticated rice will prevent the onset of neuritis or cure it when present in fowls. This extract has also been found of value

in the treatment of "taon" or infantile beriberi. Funk gave the name "vitamin" to the hypothetical substance which constitutes the neuritis-preventing principle. McCarrison believes that, while vitamin deficiency is an essential factor in beriberi, such deficiency is rarely so complete as to be the sole agency responsible for it. He considers that in the presence of avitaminosis, be it complete or partial, infections capable either of causing polyneuritis themselves or of precipitating the nerve degeneration to which the subjects are disposed, are liable to occur and to modify the features of this malady.

From this work in beriberi has arisen an entirely new conception of the value of foodstuffs, and we now recognize a series of vitamins that, according to the suggestion of McCollum, are named alphabetically. A deficiency of fat-soluble vitamin "A" leads to xerophthalmia and interferes with growth; of water-soluble "B" to beriberi and also interferes with growth; of water-soluble "C" to scurvy. It is believed that there is also a vitamin "D" which is antirachitic (Huldshinzski), and a vitamin "E" which favors reproduction (Evans). An insufficient amount of water-soluble B in the diet over a protracted period is the factor leading to beriberi. It is not the consumption of rice that constitutes the danger but rather the use as a practically exclusive article of diet of rice, or other cereal grain, from which the parts that contain the essential vitamin have been removed in the process of milling, when this vitamin is not supplied in some other article of the diet. The chemical nature or composition of the vitamin is not known at the present time.

McCollum states that there is convincing evidence that in "wet" beriberi protein starvation is superimposed upon a deficiency of the anti-neuritic substance, water-soluble B.

Many articles of diet available to the poor in beriberi zones have been analyzed and tested as to their content of neuritis-preventing principles, and with great and often surprising variations. Furthermore, the nature and importance of vitamins in diseases other than neuritis have developed rapidly and new facts that may be of value in the study of beriberi are being accumulated in many places.

Pathology.—The general nutrition of the patient varies with the stage of the disease and possibly with its type. In the early stage the general nutrition may be good, but when protracted, marked emaciation may occur. In the so-called "wet" type of the disease the anasarca may conceal a poor state of general nutrition and a good general state of nutrition may not indicate well-nourished nervous tissues.

Œdema.—All tissues may show a marked œdema. Subcutaneous œdema may be widespread or, in the early stages, confined to the lower extremities. Ascites, hydrothorax, hydropericardium, meningeal and pulmonary œdema are frequent. Numerous explanations have been offered for the œdema. It appears early in the disease before renal or cardiac insufficiency is demonstrable and when anemia is insufficient to account for it. It seems probable that the œdema may be explained by some change in the vessel walls.

Heart.—Hydropericardium may be relatively greater than transudation into the other serous sacs, or at times may be absent. Herzog found

hydropericardium present in 66 per cent. of 256 cases in the literature. Epicardial ecchymoses are almost always present. Enlargement of the heart is the rule. In the acute pernicious type this enlargement is due to dilatation, especially of the right chambers. In the more chronic cases hypertrophy also occurs and the hypertrophy of the right ventricle is characteristic. Left-side hypertrophy may also occur but is much rarer. A groove can usually be seen at the apex between the two ventricles. Antonio Sison's recent unpublished electrocardiographic findings seem to make clinical interpretation of these facts available. The heart muscle shows parenchymatous degeneration and œdema, and may show fatty change. Fragmentation of the muscle fibres and hyaline degeneration have also been described. Nagayo has seen hyaline and fatty degeneration involving the bundle of His. Scheube, Balz, Pekelharing and Winkler have described small myocarditic foci such as are found in diphtheria and other infectious diseases. Scheube has seen cellular infiltration in the subepicardial tissues and small hemorrhages in the heart muscle and beneath the endocardium. Explanation of the cardiac hypertrophy, and especially its usual restriction to the right ventricle, is difficult. Matzuoka's theory is that it is dependent upon the congestion-œdema of the lungs. Degeneration of the intramural cardiac nerves also occurs.

Lungs.—Transudation into the pleural sac occurs, but is usually not extensive. The lungs show congestion and œdema, usually most marked in the lower lobes. Aspiration bronchopneumonia sometimes occurs.

Liver.—Congestion of the liver forms a part of the general visceral congestion. Parenchymatous and fatty degeneration occur as sequels of the congestion. Nagayo described an excess of glycogen in the liver. Osborne and Mendel have shown that experimentally when an adequate supply of vitamin "B" is lacking in the diet the store of this factor in the liver tissue, where it is ordinarily found in abundance, becomes largely depleted. Suzuki has found the liver extremely large in all infants with the cardiac type of beriberi, whereas the paralytic form of beriberi does not seem to be accompanied by enlargement of the liver.

Spleen.—No characteristic changes occur in the spleen other than those due to passive congestion.

Kidneys.—These organs show the effects of passive congestion and parenchymatous degeneration. Fatty degeneration sometimes occurs. A glomerulonephritis has been described in beriberi by Miura, but the kidneys in this disease show relatively slight changes, and these changes do not account for the œdema.

Stomach and Intestine.—Wright drew attention to and emphasized the changes occurring in the stomach and intestine. He says: "The stomach and duodenum are toneless, dilated and empty. Their mucosa is deeply congested, rugæ and valvulæ are flattened and present numerous small hemorrhagic injections. Rings and patches of brilliant congestion occur and prove to be markedly dilated capillaries. They suggest sprinklings of red pepper. This congestion and injection may be found as low as the cecum; in a few instances I have found it in the ascending colon. As a rule it is most marked and occasionally wholly confined to the pylorus and duodenum. A thin pellicle of treacle-like mucus has occa-

sionally to be stripped from the congested mucosa, but no true membrane is ever formed. Infrequently the congestion proceeds to hemorrhagic erosion of the gastroduodenal mucosa. The first chain of mesenteric glands is usually swollen. Microscopically the gastro-intestinal mucosa exhibits all the signs of an acute inflammatory process." Here it is that he found his Gram-positive bacillus to which he ascribed an etiological role. In his cases of beriberi residual paralysis he says, "The stomach and small gut are generally slightly dilated, but there is a complete absence of the gastroduodenitis seen in the acute stage of the disease."

In addition to the changes described by Wright, we have found frequently in the acute cases a very marked œdema of the mucosa of the stomach and upper part of the small intestine. Intestinal parasites, have been no more frequent in our cases than in a similar class of patients suffering from other diseases.

Adrenals.—Nagayo described a progressive hypertrophy of the medulla of the adrenals in beriberi. In some of our cases a relative prominence of the adrenal medulla has been noted. Hopkins found that in rats deprived of vitamin B most organs lose weight but that the adrenal increase in size to two or three times, as McCarrison had previously shown in pigeons. Findlay found in avian beriberi a retention of lipoids in the adrenal cortex which were removed by administration of vitamin B.

Thymus.—Nagayo noted enlargement of the thymus in beriberi. Funk and Douglas maintained that in pigeons suffering from polyneuritis a marked diminution in size occurs in the glands of internal secretion. The most marked change noted by them was in the disappearance of the thymus; macroscopically no thymus could be seen in any of the pigeons with polyneuritis. Following these observations a theory that a severe change in the glands of internal secretion occurs in beriberi has been proposed by Funk on the *a priori* ground that the vitamins of the food have a close relationship to the gland of internal secretion. Williams and Crowell concluded on experimental evidence that there is no fundamental connection between beriberi and atrophy of the thymus, and that when the latter occurs in birds fed on polished rice, as it frequently does, it is due to some other cause. In our autopsy records of adult beriberi humans it is found that the thymus gland is usually small. Crowell has drawn attention to the enlarged thymus in some cases of infantile beriberi and its association with status thymicolymphaticus.

Pancreas.—No change in the pancreas has been described as characteristic of beriberi.

Lymphatic Tissue.—Nagayo noted the enlargement of the lymphatic apparatus and classified it as a progressive (restorative) change. He says that the changes in the lymphatic tissues may be due to a poison. We have found no change in the lymphatic tissues in beriberi unless associated with other stigmata of status thymicolymphaticus and we see no evidence which points to any unusual incidence of status thymicolymphaticus in beriberi.

Muscles.—Beriberi has been defined as a neuromuscular degeneration. Following, or coincident with, the nerve degeneration there occur fatty,

hyaline and colloid degeneration of the skeletal muscles. Cellular infiltration and hemorrhages between and into the muscle bundles have been described. Marked atrophy of the muscles follows.

Nervous System.—Scheube and Balz demonstrated for the first time that the essential lesion in beriberi is a degeneration of the peripheral nerves. The degeneration may be present in the central nervous system, but is most prominent in the peripheral nerves. According to Scheube, sensory and motor nerves to the muscles are most affected in the dry or atrophic form of the disease; vasomotor nerves in the wet or hydropic form, and the vagi in the acute pernicious types of the disease. The nerve endings in the muscles, as well as the nerve stems, are affected. Changes have been described in the vagi and phrenics, in the splanchnics and their visceral branches, in the solar and renal plexuses, in the nervi vasorum, in the cervical sympathetic ganglia, in the cutaneous nerves and in the nerves of the extremities. The changes in the peripheral nerves do not seem to us different in type from those occurring as the result of various organic and inorganic poisons, such as in diphtheria and typhoid fever and in alcohol, arsenic and lead poisonings.

According to Scheube, the most severe changes are in the muscle branches of the nerves. In general, he believes, that the grade of degeneration corresponds with the paralytic symptoms, the most severe changes occurring in the chronic cases, while acutely ill patients may even die before degenerative changes are demonstrable.

The change that occurs in the nerve is first a degeneration of the myelin sheath with its conversion into a fat-like substance that stains black with osmic acid. The degeneration is accompanied by a fragmentation of the axis-cylinder. Eventually the neurilemma sheath may entirely collapse, and it may show a multiplication of nuclei which is interpreted as an effort toward regeneration of the axis-cylinder. Degenerated fibres in a nerve may be very numerous, or only a few may be seen in the small part of the nerve usually submitted to examination, while the other fibres appear intact. Dürck demonstrated tigrolysis and vacuolation of the ganglion cells in the anterior horns of the spinal cord and in the spinal ganglia.

Degenerations have also been described in the fibres of the columns of Goll, Burdach and Clarke, and in the nuclei of the funiculus gracilis and funiculus cuneatus. According to Wright the cells of the bulbar nuclei and the nucleus ambiguus on both sides are swollen, with excentrically placed nuclei and a massing of the tigroid bodies.

Degenerative changes have also been demonstrated in the intrinsic ganglia of the heart, in the vagal nerve endings and in the nerve endings in other viscera. Special attention has been drawn by Japanese authors to the degenerative changes in the nerves in the vessel walls. In the meninges congestion is the rule and small hemorrhages may occur. Gato, Shizeuni and Maki assert that paralysis of nerves suffering from polished rice disease is due to the adsorption of hydrogen ions.

Souba found that in white leghorn cockerels, on a diet deficient in vitamin B and apparently adequate in all other particulars, there occurs a decrease in the size and weight of organs in the following order: testes,

spleen, heart, liver, kidneys, pancreas and thyroid gland. He also found an increased weight of suprarenals when computed per kilo body weight.

Symptoms.—The clinical manifestations may be best understood by classifying them under four varieties: (1) Usual form. (2) Severe fulminant or pernicious form. (3) Mild or rudimentary form. (4) Chronic and residual conditions.

1. **Usual Form.**—The onset usually is somewhat insidious. The patient complains of a general feeling of discomfort or, as sometimes expressed, feels toxic. There is more or less epigastric distress which varies from a sense of fulness and indigestion to more or less actual pain. The patient tires easily and there may be headache of a dull, heavy character. This prodromal stage may last from one to two or three days. Frequently the disease seems to be brought out during some slight indisposition, such as a "cold," diarrhœa, slight fever or fatigue from prolonged exertion. In these circumstances there are no prodromal symptoms which may be positively charged to the neuritis. In any case the characteristic symptoms develop quite rapidly, so that the typical clinical picture is established within two or three days, although it may be delayed for a week. In the order of development the symptoms do not follow a fixed rule. Usually, heaviness, numbness and more or less pain develop in the legs. This is noticeable on walking, from which the patient quickly tires. Numbness and paresthesias develop first in the calf muscles, to be followed by pain on motion and tenderness on pressure. Cramps in the calf muscles occurring especially in the morning is one of the most frequent and constant symptoms of beriberi (Antonio Sison). Œdema, noticeable first as slight pitting over the lower tibia, progresses gradually over the legs and feet and later to other parts of the body, particularly the hands and face.

Usually the epigastric symptoms are considered to be indigestion, and this frequently is the complaint which takes the patient to a physician.

As the disease progresses the leg pains become decided, particularly on motion or pressure; the joints feel as if they were out of control; the numbness may extend to the hands, arms and face; the œdema becomes noticeable in the face and hands; a general sense of depression and oppression is complained of and the gait becomes characteristic; within a few days the patient is no longer able to walk or to stand without assistance. The patellar reflexes at the onset frequently show a transient period of increased excitability, but they quickly become markedly diminished and finally lost. The superficial reflexes usually remain normal.

In the fully developed stage the patient stays in a fixed position because motion increases the pain; the face and more or less rapid respiration indicate embarrassed circulation. The facies in general is that of an ill patient, the skin varying from normal to more or less cyanosis, the face, legs, feet, hands and frequently other parts of the body showing more or less œdema; the respiration and pulse are accelerated. There is epigastric distress, pain and tenderness in the legs, and sometimes in the upper extremities. Numbness and paresthesias are unevenly distributed and more extensive than the pain areas. The urine is diminished and not

infrequently there is some looseness of the bowels. Nausea and even vomiting may be present.

A patient at this time shows *tachycardia* due to myocardial changes and influenced in some cases by more or less fluid in the pericardial sac. The rapid respiration may be due to embarrassed circulation, or there may be some fluid in the pleural cavities, and there may be a cough with considerable fluid expectoration. There is tenderness over nerve areas, more marked in the calves, and usually pain is much increased on motion of the lower extremities. The patellar reflexes are absent. There is nothing significant in the urine or blood.

The patient may continue in this condition for days or weeks, with but slight change. In fatal cases the symptoms grow worse, the pulse increases in rate, the œdema extends, more fluid is found in the serous cavities and the patient finally succumbs to cardiac failure, less frequently to paralysis of respiration, or sometimes to acute pulmonary œdema.

In patients who recover, the symptoms subside slowly, frequently in reverse order to their appearance. As the circulation improves and the œdema subsides the muscle wasting becomes apparent. Convalescence is exceedingly slow, lasting frequently for many months, and sometimes complete restoration of function is never attained.

There may be considerable variation in what we have termed the usual type. All of the symptoms may not be present in a given patient and the order of their appearance may vary. In one patient the epigastric symptoms may be the most pronounced and annoying, in another the cardiac symptoms may predominate, and there is frequent and marked variation in the extent and amount of the œdema. In fact the œdema may be so slight and temporary that the "dry" stage may be considered to be primary. Some authors consider that the dry form does develop primarily without there ever having been œdema.

2. **Severe, Fulminant or Pernicious Form.**—This differs from the preceding form chiefly in the intensity of the disease and the early and fatal heart failure. The onset usually is sudden, The whole cycle of the disease may be completed within one day, although the average duration is two to five days. It may develop out of a previously milder case.

This type of beriberi is a veritable plague, with very acute symptoms and a rapid course, and practically is always fatal. It rarely occurs sporadically but in prisons and overcrowded places where the disease is epidemic. The nature of the symptoms and the order of their appearance frequently is much the same as in the usual type, but much intensified. The circulatory features are most striking and characteristic. They appear early and are the first and sometimes practically the only ones present. At first there is tachycardia followed by increased respiratory rate, cyanosis, rapid heart failure and death. Œdema of the lungs may constitute the terminal condition.

From first to last the clinical picture may not be distinguishable from that of acute progressive myocardial insufficiency from other causes. The expression shows anxiety, the skin is moist, the eyes staring and the pupils dilated; heaving chest motion and diffuse palpatory thrills are present.

Epigastric distress with vomiting is early, severe and constant. When the disease is a little less malignant and patients live more than two or three days the clinical picture may approach more nearly that of the usual type. The œdema has time to develop and the clearer intelligence allows a keener appreciation of pain and other subjective symptoms. The accumulation of fluid in the serous cavities is noticeable, the urine is diminished, and there is thirst and loss of appetite.

3. **Mild or Rudimentary Form.**—The onset is insidious. The earliest symptoms consist in a feeling of languor, a dull, stuffed sensation in the epigastrium, heaviness, numbness and some tingling about the calves. The sensations in the legs frequently are more noticeable in the night or early morning, particularly during the cooler season, when after hot days there is quite a decided chill in the early morning hours. Examination of a patient at this time shows slight but definite tenderness of the calves, slightly exaggerated or more generally definitely diminished patellar reflexes and possibly some acceleration of the heart. In the majority of instances the patient will show slight but definite disturbance in the gait, consisting of hesitation in lifting the foot and an uncertainty or delicacy or deliberateness in placing it again. One rarely sees this stage in hospital or private practice, but in the ambulatory patient clinics for the poor it is encountered with great frequency. Unless the disease advances beyond this point there may be a question as to whether or not it really is beriberi. Most of these patients are teamsters, laborers, rice-workers and others whose occupation keeps them outside, and they attribute the condition to getting wet suddenly while exposed to heat.

As the disease progresses, the pains in the muscles of the legs, particularly the calf muscles, become more pronounced. These pains are spasmodic, cramps, and during the intervals between pains paresthesias are more or less constant. There is often a constant soreness of the muscles and weakness of the legs is complained of after a few days or weeks of the disease. Other symptoms are dizziness, increased by exposure to the sun or by close application of any kind, slight epigastric distress and frequently some slight nausea. *Objectively* not much is found. The calf muscles and often others are tender on pressure and the patellar reflexes are sluggish and sometimes absent. Œdema is slight or absent and examination of the heart may be negative. The blood, urine and fæces do not show anything definite.

The disease lasts from a few weeks to months and even years unless treatment is instituted. Under rest in bed or confinement to the house, appropriate food and a bitter tonic recovery is rapid. Apparently one attack does not confer immunity but rather seems to increase the susceptibility. We have seen the same patient with as many as three attacks in one year. During the protracted period of invalidism the patients hobble about, eke out an existence in various ways and alternate in "cures."

Muscular spasms and cramps of the legs with some paresthesia, noted more during cool nights, is not by any means confined to the Orientals. Many Occidentals who have resided in the tropics for years are sufferers from it. In many instances the exceedingly mild condition takes on other

symptoms which are definite and leave no doubt of the diagnosis of a neuritis.

4. **Chronic and Residual Conditions.**—Except in the acute fulminant type the natural tendency of beriberi is toward chronicity. It is primarily a long drawn out, slowly acting process, with acute exacerbations and tedious recovery, blending often into residual conditions which may be permanent and disappear, if at all, very slowly. The extent of incapacity varies from those slightly crippled with leg cramps and tachycardia on exertion to completely helpless invalids, emaciated and miserable with pain.

After all activities of disease have subsided the residual paralysis, muscle atrophy and cardiac hypertrophy and dilatation remain for long periods and it not infrequently happens that complete restoration of form and function never takes place.

Analysis of Symptoms.—*Gait.*—The gait is characteristic principally in that it differs from the various ataxias and spastic gaits of well-known diseases. It differs somewhat in accordance with the nerves involved, and consequently the corresponding varieties of muscle atrophy. True ataxia is never seen, but a spastic gait resembling that of spastic spinal paralysis may occur during convalescence.

Disturbances of Motor Function.—All stages of muscular inefficiency are encountered, from numbness and sluggish action in mild cases to complete paralysis in the severe prolonged cases. There is selectiveness and variety in muscular involvement corresponding exactly to the distribution of affected nerves. In the order of frequency the muscles of the feet, legs, hands and arms are involved; beyond various muscles of the face and body those of most importance and serious consequence being the diaphragm and heart muscles. The sphincters are not involved. The electric reactions are similar to those in peripheral neuritis due to other causes. Paralysis of the vocal cords, says Antonio Sison of Manila, (personal communication) has been observed in some instances, giving rise to hoarseness or aphonia.

Vasomotor and Sensory Changes.—Paresthesias of many types and varying forms from complete anesthesia to the most intense hyperesthesia always form a part of the clinical picture. Those most prevalent are localized anesthetic areas corresponding to the areas most involved in the disease. The lips and tongue are paresthetic, frequently without signs of muscular insufficiency. The physical conditions of cold, moisture, pressure, etc., that affect paresthetic areas apply here. In interpreting phenomena of anesthesia and paresthesia it is well to remember that many beriberi patients are not keenly responsive to our ordinary testing methods and unless care is used errors are liable to occur, particularly in interpreting anesthesia. Vasomotor dilatation of the superficial vessels of the skin may lead to the most pronounced perspiration, and rarely an erythematous blush in affected areas may be seen among the lighter-skinned patients.

Reflexes.—The patellar reflex may be increased for a brief period at the onset. In all established cases it is either decidedly diminished or more frequently entirely absent. Altered patellar reflex usually is one of the

earliest signs to appear and among the last to be restored to normal after recovery.

Circulatory Disturbances.—*Tachycardia* in varying degrees is constant. In mild cases it may be scarcely noticeable on resting and only shows an exaggeration reaction from mild exercise. In more severe cases it becomes prominent, causing anxiety to the patient, who can feel the increased rate and labored action of the heart. Frequently there is precordial pain. The heart symptoms are due to myocardial changes, with dilatation more marked on the right side but later involving both ventricles.

Œdema and the collection of fluid in the serous cavities to a greater or less extent occurs in most cases of the disease at one time or another. The frequent presence of dry atrophy as opposed to œdema may be striking throughout the course. The more or less complete change from "wet" to "dry" varieties in the same patient is not easily explained, except by assuming some influence in the etiology. McCollum thinks this influence to be protein starvation superimposed upon a deficiency of vitamin causing the "wet" variety.

The accumulation of fluid in the pericardium or pleural cavity may be sufficient to cause serious consequences. The amount in the abdomen and elsewhere is smaller, but there usually is some in all serous cavities, at least in acute cases of the disease. The œdema usually appears first in the feet and legs, hands and arms, then the face, and later in severe cases one sees a striking picture of general anasarca. Pulmonary œdema is not an unusual form of termination of the acute disease.

Fever is not due to beriberi and when present is due to some associated condition.

The systolic *blood-pressure* is generally lower in the tropics, both among natives and foreign residents, than in temperate climates. Even taking this into consideration the records seem to show that beriberi produces a lowering in the systolic pressure. This was true in the experimental cases of the disease studied by Strong and Crowell.

Blood examinations show little that is characteristic. What departures from normal there are may be explained by associated conditions. A number of writers have called attention to a relative mononuclear increase of varying degrees, but Chamberlain and Vedder and others believe that the relative increase in the lymphocytes is a pretty general condition in the tropics. Nagayo on the other hand believes that lymphocytosis is an established change in the blood in beriberi and is a valuable distinguishing point between this disease and polyneuritis gallinarum.

Basal Metabolism.—Okada, Sakurai, Ibuki and Kabeshima found that the basal metabolism usually shows normal values, but that in some cases a marked diminution appears in the course. Fleming found no alteration in the basal metabolic rate in beriberi patients.

Alimentary System.—Epigastric discomfort or distress is frequently an early symptom—sometimes the very earliest—in the disease. These symptoms are probably due in part to more or less disturbance in the duodenum and in part to interference with digestion. They may be entirely absent. Nausea and vomiting may be distressing in fulminant

cases and are fairly frequent in less serious forms. Diarrhœa and other forms of intestinal disturbance are not important.

Urinary System.—The most important feature is the variation in the quantity of urine excreted. Frequently in severe types the quantity is much decreased, and it may cease altogether before death. At times in the dropsical form there may be a very marked increase in the quantity of the urine, a change usually simultaneous with the reabsorption of fluid from the œdematous areas. There are no characteristic routine changes in the urine.

Diagnosis. In endemic zones there is usually no particular difficulty in arriving at a diagnosis of multiple neuritis. Unfortunately only too often the diagnosis of neuritis is accepted as synonymous with beriberi. The differentiation between beriberi and multiple neuritis of other etiology is not easy to make by direct examination, and is only justified after a painstaking and thorough investigation into the etiology of each case. Recently Antonio Sison (unpublished) has found that right ventricular preponderance in the electrocardiographic record is uniformly present in beriberi and is of diagnostic importance in distinguishing beriberi from other types of neuritis.

Beriberi is perhaps most frequently confounded with alcoholic neuritis. This mistake is made easy by the unfortunate statement so frequently made that Orientals do not take alcohol.

Differentiation from various other dropsies and œdemas ordinarily is not difficult. However, it seems advisable to call attention to the mechanical difficulties encountered in examining the reflexes in patients already with much œdema, particularly of the legs.

Prognosis.—The mortality rates, as in all other pandemic and endemic diseases, vary greatly as reported from different countries, as well as from different localities in the same country. The mild form rarely is fatal, but it often changes, and quickly, to a more severe one with higher mortality, and this potential danger must be recognized. The acute fulminant type is practically always fatal. Mortality in the usual form vares from 2 to 60 per cent. as given by different authors and representing statistics from different endemic zones.

Prophylaxis.—Whether considered from a public health, social or medical standpoint the prevention of tropical neuritis is a large and urgent problem. More than half the population of the world lives within the endemic zone and the disease must be eliminated before great permanent progress will be made in the development of many countries.

The task of providing the essential remedies of better homes, better food and cleaner living is a disheartening one. Temporary improvement may be achieved in local areas by organized government and other charities, but this further pauperizes the people and is an impossible permanent solution on a large scale from an economic standpoint. Compulsory control over the lives and activities of the people has been employed in places. It is an effort of doubtful utility and one not free from danger. Permanent results may be achieved only by instilling attributes of thrift, energy, cleanliness and physical development into the people. To do this involves the expenditure of large sums of money; requires a firm,

non-political government and the constant directing influence of skilled advice over several generations. The energetic, thrifty, clean-living citizen is at present a tropical exotic, and the propagation of a population of this class is only in the making. Certain things, however, may be done, and the most important is to secure by the best and most practical means applicable to any given community such improvement in the food supply as is possible. This may be done, as in the Philippine Islands, by teaching gardening in the public schools and encouraging the cooking and use of a wider variety of good home-grown foods.

There is no doubt that "undermilled" rice is a safer article of diet than that with all the pericarp removed, and under circumstances where it is the chief available foodstuff for the poor, every possible effort to secure its use should be employed. Enforced use of whole rice may, of course, be employed by the military authorities and in prisons and other institutions under complete control, but compulsion should not be attempted among a people who have a voice in their own affairs. The Philippine experiment illustrates this point: Although unmilled rice is not delectable to a rice lover, it might have been made popular, just as the Bureau of Education made the use of maize popular, except for the great and widespread resentment created by enforcing its exclusive use among soldiers, lepers and prisoners.

Nations holding colonial interests within the endemic zone of tropical neuritis can render a great service to humanity by studying the local problems and applying methods that will ensure the universal use of a better and more varied diet than exists in those countries at the present time.

Treatment.—The treatment of beriberi is symptomatic and specific. The vast majority of patients are too poor to buy medicines, and when they do succeed it is at the sacrifice of food for themselves and perhaps their children. A clean bed in a light sanitary room and proper food will cure more of these patients than medicine, and it is less expensive. A glass of milk is a better "tonic" than all the drugs in the pharmacopœia.

Among the better-class patients the refined methods of symptomatic treatment may be instituted. The circulatory, urinary and digestive functions should be watched. Strychnine, digitalis, atropine, and various heart stimulants have been recommended to guard against or relieve existing circulatory or respiratory embarrassment. They are of doubtful value. Absolute quiet in bed with an ice-bag over the heart will do much to prevent the necessity of treating urgent heart symptoms. Squill, citrate of potash and other similar remedies are used to increase the urine secretion, but are of doubtful value. Small doses of concentrated solution of magnesium sulphate are indicated when a laxative is necessary.

Specific Remedies.—Quite a variety of drugs from time to time have had more or less vogue as specifics. It may be safely stated that none of them has any such properties.

Due largely to researches during the last few years, decided progress has been made toward specific treatment of the disease by the use of appropriate foods and particularly by the use of extract of rice polishings and other substances rich in vitamins. Some of the reports of the results

of this method of treatment have been overly enthusiastic, but definite progress has been made and a sound foundation for further investigation established. As a result of much careful work in the Philippine General Hospital in Manila, José Albert, Antonio Sison and others believe extract of rice polishings to be a specific in the treatment of infantile beriberi, but a failure in the disease in adults. Further application of the newer knowledge of vitamins in the treatment of food deficiency neuritis offers a promising field for competent students.

Osborne, Mendel and Wakeman have shown fresh fruit juices, especially those of orange, lemon and grapefruit, to contain water-soluble vitamin B in quantities as potent as comparable volumes of cow's milk. Foods that have been found to contain vitamin B in appreciable amounts are milk, eggs, glandular organs, whole cereal grains, tomatoes and most fresh green vegetables and tubers, yeast, germinating seeds and nuts.

Willcox reports that good results in treatment followed the addition of extract of yeast to the diet, and the addition of wheat rich in vitamin B to the bread, for the use of British soldiers during the Mesopotamian campaign in 1916 and 1917.

INFANTILE BERIBERI

That there is a serious cause or group of causes effective in beriberi zones to which prospective mothers and infants both before and after birth are particularly susceptible seems unquestioned. The disease (or diseases) is widely recognized among experienced physicians as infantile beriberi. It is blamed—and probably correctly—with being an important factor in the unusually high infant mortality—prenatal and postnatal—that is found so universally in beriberi zones. Etiologically this condition usually more nearly approaches the true picture of a nutritional deficiency than does the adult disease, and recent reports confirming the previous claim that extract of rice polishings is specifically curative lend support to the nutritional deficiency origin of the trouble in infants. Symptomatologically and pathologically the infantile variety closely resembles the severer forms of the disease in adults. Some of the lack of greater unanimity of opinion regarding the incidence, diagnosis and treatment of this condition is due to the same limitations in our diagnostic methods that apply to the consideration of the forms of tropical neuritis as a whole and of beriberi in particular.

CHAPTER XXVII

SCURVY (SCORBUTUS)

By ROBERT HUTCHISON, M.D., F.R.C.P., (Lond.).

Scurvy may be defined as a disease of deficiency due to the absence from the diet of a specific vitamine and characterized by debility, mental apathy, and anemia, with sponginess of the gums, ulceration of the mouth, and a tendency to hemorrhages into the subcutaneous tissues and from mucous surfaces.

Etiology.—It is now established that scurvy is due to the absence of a specific vitamine (water-soluble C) from the diet. The view that the disease is caused by poisoning with ptomains has been abandoned, nor has the infective theory gained many supporters. The hypotheses that it results from a deficiency of potash salts (Alfred Garrod) or of alkaline compounds (Wright)in the diet have also failed to stand the test of criticism. Axel Holst first succeeded in producing the disease artificially in animals (1907) by feeding them on a scorbutic diet and his experiments have been amply confirmed. The vitamine is present in *fresh* vegetables and fruits and to a less extent in meat juice and milk. It is destroyed by heat, by drying and by alkalis; it is protected by acids. It is soluble in water and in alcohol.

Morbid Anatomy.—The bodies usually exhibit only a slight degree of rigor mortis, and putrefaction occurs early. The only constant morbid change is effusion of blood in various situations. These effusions, which may be diffuse or circumscribed, are met with both in the skin and subcutaneous tissues and under the periosteum of the bones. They consist of altered blood which may have undergone partial clotting or even organization into fibrous tissue. Hemorrhages are also met with in the pleura and pericardium and, though more rarely, in the peritoneum as well. There may also be hemorrhagic effusion into the joints. The internal organs show no constant change, but the heart muscle is soft and often degenerated. The lungs are œdematous, and may contain infarctions. The kidneys and liver rarely exhibit any signs of disease. The spleen is large, soft, and congested, and may also show infarcts on its surface. It is important to note that all accurate observations agree in showing that the bloodvessels exhibit no gross or microscopic changes.

In the altered gums, Babes distinguishes five layers: (1) A surface layer, for the most part free from epithelium, moderately thick, pale, resembling a diphtheritic membrane with a few fragments of nuclei, and containing various bacteria, especially streptococci. (2) A structureless layer, about 1 mm. thick, consisting of a felt-work of long fine bacteria. (3) Uni- and multinucleated round cells. (4) A layer of

œdematous mucous membrane containing many bacilli resembling those in the second layer. In the walls of the vessels are numerous swollen spindle cells. (5) Large and much dilated vessels with large spindle cells in their walls. In the blood which fills the vessels are cell masses, numerous multinucleated leukocytes, endothelial and mast cells but no bacteria.

Symptoms.—*Prodromal Symptoms.*—Scurvy is usually a disease of insidious onset and from four to eight months on a scorbutic diet may elapse before it sets in. The patient begins to suffer from loss of bodily vigor, and from an even more marked mental apathy and lassitude so that the slightest task becomes a burden. At the same time he looks ill. The face becomes pale, or sallow and drawn, the eyes sunken, lustreless and encircled by dark rings and there may be follicular keratosis of the skin. At this period, there may be some pitting of the ankles on pressure and a tendency to diarrhœa, while it may be observed that the least knock or injury tends to be followed by a bruise. He suffers also from pains in the limbs and joints. Night blindness may occur. To these symptoms there are soon added those characteristic of anemia—shortness of breath on exertion, palpitation, and a tendency to syncope.

Such symptoms may precede by a few days or even weeks the more characteristic signs. Among these the most striking, though not necessarily always present, are the changes in the *mouth*. The gums begin to swell especially around stumps or carious teeth, and as the process goes on the swelling may become so great as to amount to a veritable hypertrophy, so that the teeth become buried in a mass of soft, fungous tissue of a bluish or purplish tint. Ulceration quickly follows along the margins, the process being accompanied by the discharge of a sanious fluid which imparts an odor of great fetor to the breath. Finally the teeth become loosened in their sockets and may fall out, while necrosis of the alveolar edges ensues.

Equally characteristic and constant are *hemorrhages into the skin* and *subcutaneous tissue* which assume the form either of petechiæ or of ecchymoses. The former occur as small red or purple spots which appear first around the hair follicles of the lower extremities and impart, by the elevations which they produce, a slight feeling of roughness to the skin. They remain for about a week, and then gradually fade into greenish spots which soon disappear; their disappearance being followed by a slight degree of desquamation. The production of the petechiæ is determined by the slight irritation caused by the friction of the clothes, and hence they are always found first on the outer surface of the leg, and the outer and anterior aspects of the thigh. Here and there the petechiæ may coalesce into larger areas. In severe cases the slightest pressure on the skin is sufficient to cause ulceration, the ulcers having thick edges and bleeding surfaces with offensive discharge. Such ulcers may spread rapidly and invade surrounding tissues, giving rise in some cases to dangerous, and even fatal hemorrhage. *Ecchymoses*, the other characteristic surface lesion of scurvy, are produced by hemorrhage into the subcutaneous or intermuscular tissue. They may occur spontaneously or as the result of injury, and vary greatly both in size and extent, being com-

monest in the lower extremities, where they may form quite large swellings. The part affected is brawny, tender, and pits on pressure, the indentation persisting longer than in ordinary œdema. The skin over them is red, shiny, and hot. Such effusions are common, also, in the popliteal space and in the bend of the elbow, as well as in the loose tissue around the malleoli, and beneath the muscles of the jaw. In these situations they form indurated swellings which fill up the natural hollows of the part, and greatly interfere with the movements of the adjacent joint. Where such effusions occur over the shins, they are apt to be mistaken for syphilitic nodes.

There is no marked tendency to bleeding from the internal organs but hemorrhages may take place from the mucous surfaces. Of such hemorrhages, epistaxis and bleeding from the mucous membrane of the mouth are commonest. Bleeding may also occur from the mucous membrane of the intestine when there is a coëxisting diarrhœa. Hemoptysis, hematemesis, and hematuria are rare. Hemorrhagic effusion into the pleura and pericardium has also been described. Not uncommonly hemorrhage occurs under the conjunctiva, and may be so extensive as appreciably to raise the ocular layer, leaving the cornea at the bottom of a pit surrounded by swollen and red conjunctival membrane.

As the disease progresses *anemia* becomes a marked feature. The red cells are much reduced and exhibit poikilocytosis and anisocytosis; the color index is variable. Nucleated red cells are only present in very severe cases. The white count varies. In some cases a moderate lymphocytosis has been observed, in others a leukopenia. A leukocytosis is present if inflammatory complications exist. Blood cultures are sterile, the serum is not hemolytic and the coagulation-time is unaltered. The alkalinity tends to be reduced.

Alimentary symptoms are often absent. Appetite is not necessarily impaired, but dyspeptic symptoms may be present as the result of the imperfect diet which produces the disease. Constipation is the rule, but the conditions under which scurvy is developed frequently favor the production of diarrhœa of a dysenteric type, and when such a complication exists it may be attended by bloody discharges from the bowel.

The *urine* at the outset is scanty, high-colored, turbid, and occasionally albuminous, but as improvement sets in it becomes more abundant and pale. The amount of free acid in it is diminished, and so, it is alleged, are the potash salts.

Of the **complications**, gangrene of the lung is one of the most frequent and dangerous. It is marked by the usual expectoration of dark fetid matter, by rapid and difficult breathing with great depression, and usually ends fatally.

Buzzard described a condition which may be mistaken for pneumonia. Faint rigors, followed by a certain amount of feverishness and accompanied by lancinating pain in one or both sides, usher in this condition. The pain is felt only on coughing, and a very viscid mucus is expectorated. The dyspnœa increases, and a constriction, as though from a cord bound tightly around the chest, is described. Although occasionally these pulmonary symptoms are dependent upon true inflammation, they are

much more commonly associated with the effusion of sanguineous fluid into the cavity of the pleura or into the substance of the lung itself, these structures sharing that tendency to effusion which is the dominant feature of scurvy. When the lung is thus invaded the expectoration after a short time becomes dark and sanious, with all the horrible fetor which is ordinarily associated with gangrene of the lung, but which is here dependent upon decomposition of the bloody fluid poured into the lung substance. There are cold sweats, increasing dyspnœa and anxiety, a small and frequent pulse, and death. In other cases there is no pain or cough, but the breathing rapidly becomes short and labored, and death occurs suddenly. Auscultatory signs in the lungs are usually wanting, but now and then there is localized dulness on percussion with bronchial breathing, or mucous rales are heard, sometimes with gurgling sounds at certain parts of the chest.

Night blindness is sometimes met with in patients suffering from scurvy who have been much exposed to bright light, and may occur quite early in the disease. It would appear to be merely the result of anemia and exhaustion and not an essential part of the scorbutic process.

Diagnosis.—If all the characteristic symptoms are present and if the disease arises simultaneously in a number of subjects in circumstances known to favor its development, the diagnosis is easy. Difficulty only occurs when one has to deal with sporadic cases, such as the cases of land scurvy occasionally met with in badly fed individuals.

The disease which perhaps most closely resembles it is *purpura hæmorrhagica* (*morbus maculosus* of Werlhof), but in this the affection of the gums is absent and the hemorrhages have not, as they have in scurvy, an inflammatory character. *Mercurial cachexia*, which in many points closely simulates scurvy, is now but rarely seen and an inquiry into the history will usually lead to a correct conclusion. *Acute lymphatic leukemia*, which is often marked by ulceration in the mouth, can be distinguished by an examination of the blood.

Prognosis.—This, except in the severest cases, is favorable, provided suitable treatment can be adopted. It has often been noted that the outlook is by no means dependent upon the severity of the lesions in the skin, mouth, and muscles, but is in far closer relation to the state of the internal organs such as the lungs and heart. The supervention of the complications and of intercurrent disease also exerts a powerful influence upon the prognosis while a speedy and often unexpected fatal result may be brought about by severe hemorrhage or heart failure. Even in cases which run a favorable course it may be weeks or even months before the patient is restored to his original vigor, and when recovery is complete there may still be some results shown in cicatrices in the skin or partial ankylosis of joints.

Treatment.—The first point is to remove the patient if possible from the place in which the disease has developed and to bring him under more hygienic conditions. Cold and damp should especially be avoided and he should be placed in warm and dry surroundings. Of even greater importance is a radical alteration in his diet so as to supply a sufficiency of the antiscorbutic vitamine. Fresh vegetables and fruits—especially

the juice of oranges, lemons, and grape-fruit—should be given freely. Among vegetables, cabbage (raw or cooked) potatoes, onions and the juice of swedes are specially valuable. Germinated pulses and cereals also contain the vitamine.

Preserved vegetables, though useful, seem to have a feebler anti-scorbutic power than fresh; sauerkraut appears to be more serviceable in preventing the disease than any other form of preserved vegetable, and Captain Cook employed it successfully in some of his voyages. Canned tomatoes are of considerable value. Infusions of malt are also powerfully antiscorbutic. The infusion should be fresh, for its good qualities are impaired if it is allowed to become damp and mouldy.

Fresh meat juice has been found to be of value as an antiscorbutic, and fresh milk is also serviceable; dried milk has some antiscorbutic power but condensed and citrated milk have not. Of beverages, French and Italian wines are stated to be antiscorbutic, but opinions as to the power of cider in this respect vary considerably.

Drugs have no influence upon the disease, but the administration of bitters, especially quinine, and of iron to combat the anemia is of help in restoring health, and special complications may require appropriate remedies.

Locally the mouth conditions demand attention. Antiseptic washes of permanganate or chlorate of potash or peroxide of hydrogen help to remove the fetor, while the spongy and ulcerated gums may be painted with a solution of nitrate of silver (2 to 3 per cent.). Absorption of local effusions of blood may be promoted by gentle massage.

The *prophylactic treatment* consists in attention to general hygienic conditions and in the provision of an abundant and varied dietary containing an adequate proportion of vegetables and fruits.

So-called lime juice has been used as a prophylactic but it is now known that real lime juice in its preserved form is not antiscorbutic and that any effective preparation was really made from lemons. Tablets of fresh lemon juice are a convenient form of antiscorbutic for use on board ship.

INFANTILE SCURVY

That infantile scurvy is due to the same cause as the adult form of the disease there can be no doubt. None the less, the clinical manifestations of the two forms are very different, but the differences are probably to be explained by differences of diet and by the anatomical and physiological peculiarities of the infantile period of life.

History.—Infantile scurvy was really described by Glisson in his *Treatise on the Rickets* published in 1651, but the disease was lost sight of for two centuries when it was described by Continental writers under the title of "acute rickets." Cheadle first pointed out its identity with adult scurvy in 1878, and five years later Barlow secured general recognition for the truth of Cheadle's views by a paper which has become a classical publication and has caused infantile scurvy to be generally known on the continent of Europe under the name of "Barlow's disease."[1]

[1] *Trans. Royal Medical and Chirurgical Society*, 1883, **66**, p. 159.

Etiology.—The vast majority of cases of scurvy arise in infants who are being fed on a diet which is deficient in *fresh* constituents and is therefore poor in antiscorbutic vitamines. The diet which most commonly produces the disease seems to be one consisting of condensed milk with the addition of a tinned food, but a diet of sterilized milk alone is undoubtedly capable of giving rise to it, and so even may milk which has merely been boiled. Griffith,[1] in summarizing the results of an investigation of 356 cases collected by a committee of the American Pediatric Society, with the addition of 18 cases of his own, concludes that in 60 per cent. a proprietary food had been used but often with the addition of sterilized milk. Nine per cent. had been fed on condensed milk and 19 per cent. on sterilized milk only.[2] Pasteurized and dried milks seem much less apt to produce the disease. Occasionally scurvy has developed in babies fed at the breast. This is probably due to a deficiency of vitamine in the mother's diet.

Morbid Anatomy.—The chief changes are present in the neighborhood of the bones. If a section be made across a limb which has been the seat of swelling during life it will be found that the periosteum is thickened, highly vascular, and separated from the subjacent bone by a layer of blood clot which may show various degrees of organization. There is no sign of inflammation, and, as a rule, no hard bone is formed in the periosteum except in very old-standing cases. The muscles surrounding the bone may be infiltrated with blood or serum, which gives them a sodden appearance. The bone exhibits a considerable degree of rarefaction, the cancellous tissue being unusually porous and the normal marrow replaced by a highly vascular connective tissue into which hemorrhages may have occurred. The changes characteristic of rickets may also be present in the bones. The rarefaction of the bone is apparently the result of delayed ossification and is the cause of the fractures not uncommon in severe cases and which are usually situated a little above the epiphyseal line, although there may sometimes be separation at the line of the epiphyseal cartilage itself.

Hemorrhagic effusions may be met with elsewhere in addition to those around the bones, such as in the joints or in the serous cavities or subdural space. None of these, however, is characteristic of the disease. The internal organs exhibit no constant change.

Symptoms.—Scurvy is commonest in infants of about eight to ten months old, which is in keeping with the fact that it takes several months on a scorbutic diet to produce the disease. The children affected are usually well-nourished, but often exhibit some degree of pallor. The invasion may be either gradual or abrupt. After a few days of fretfulness or after having exhibited for some time great tenderness when handled, the more prominent symptoms appear. The most striking of these is *tenderness* of the legs, which causes the child to scream when touched or even at the approach of the doctor. The child lies very still, usually on his back with one or both legs everted and motionless. Examination

[1] *New York Med. Jour.*, 1901, **73**, 317.

[2] For additional evidence of the production of scurvy by sterilized milk, see Netter, *Rev. des Maladies de l'Enfance*, 1902, **20**, 543; Neumann, *Deutsches. med. Wchnschr.*, 1902, **28**, 628, 647; and Ashby, *Brit. Med. Jour.*, 1904, i, 479.

in a well-marked case reveals some swelling of the bones, most commonly of the lower end of the femur or upper end of the tibia. The long bones of the upper extremities are much more rarely affected, the collective investigation in America yielding only 14 cases with swelling in the arms, to 131 in which the legs were affected. At the site of these swellings the tenderness is extremely acute and the skin over them is often tense and glossy, and may be slightly œdematous, but there is no local heat. On gently handling the limb soft crepitus may be elicited, from fracture or separation of the epiphysis. In some cases hemorrhage takes place into the orbit, giving rise to proptosis and ecchymosis of the eyelids. This occurred in 49 out of 379 of the American cases. The proptosis may appear suddenly, often during a fit of crying, and in severe cases may lead to ulceration of the cornea.

Rarer sites of hemorrhage are around the ribs, clavicles, or bones of the skull. Sir Thomas Barlow described a peculiar depression of the sternum *en bloc*, which is present in severe cases and is apparently due to a loosening of the articulations between the sternum and ribs.

Changes in the Gums.—These are not usually present unless some teeth have been cut, but even in the absence of the latter there may be a slight degree of injection and ecchymosis, especially over the sites of the incisors. Should any teeth have erupted, the gum around them is usually swollen and of a purplish color, but the change is rarely if ever so marked as in the scurvy of adults and does not often go on to ulceration. It is rare for the gums to appear normal after any teeth have appeared, but a few such cases have been observed.

Other Symptoms.—Petechiæ and subcutaneous ecchymoses are rarely met with in infantile scurvy and hemorrhages from mucous surfaces, with the exception of the gums, are not common. Hematuria is met with not infrequently and a slight degree of it, at least, is probably much commoner than is generally believed. Sometimes it is the only symptom present and in a few cases it appears to lead to nephritis or pyelitis. Fever is not a conspicuous feature, but when extensive hemorrhages have taken place there may be a rise of temperature, which, however, rarely exceeds 101° or 102° F.

Blood.—There is usually some anemia, especially in cases in which extensive subperiosteal hemorrhages have occurred. The anemia is usually of the chlorotic type, the hemoglobin being reduced out of proportion to the red cells, but where the hemorrhages have been especially severe the characters of a secondary anemia may be exhibited, and the red cells are reduced in number and some nucleated forms present. In the absence of complications no leukocytosis occurs. In a series of cases examined by the writer no alteration in the coagulability could be discovered. Whether or not there is any reduction of alkalinity has not been determined.

Association with Rickets.—The relation of scurvy to rickets has been much disputed. That the two conditions are not invariably associated is shown by an analysis of 40 fatal cases by Schoedel and Nauwerk,[1] in 18 of which the presence of rickets had been recognized during life,

[1] *Rev. des Maladies de l'Enfance*, 1902, **20**, 543.

while it was found in 3 others after death. The frequent coëxistence of rickets in cases of scurvy would seem indeed to be due merely to the fact that the kind of diet which produces the one disease also tends to give rise to the other.

Diagnosis.—This is easy in a well-marked case provided the leading features of the disease are known to the observer. The screaming of the child on examination, the swelling and tenderness of the legs, and the condition of the gums leave no doubt as to the nature of the affection. All cases, however, are not so pronounced in type. Not infrequently one encounters mild or incipient forms which it is easy to overlook. In these, tenderness when the child is handled or when he is put in his bath may be the only symptom. In other cases slight sponginess around the incisor teeth may alone be present or one may have to deal with an apparently causeless hematuria. In any case in which there is doubt two points will help. One is the nature of the feeding. If this has been of such a nature as is known to favor the development of the disease the diagnosis will be greatly strengthened. The other point is the application of the therapeutic test. If the symptoms present are really due to incipient scurvy then they will certainly disappear rapidly so soon as appropriate treatment is begun; if they fail to do this then one has to do with some other condition.

The affections for which scurvy is most often mistaken are these:

1. *Rheumatic Fever.*—Time and again the writer has had well-marked cases of infantile scurvy sent to him with this diagnosis. The mistake should not be made if it is remembered that below the age of one year rheumatic fever is never met with.

2. *Periostitis.* The distinction between scurvy and periostitis is often difficult, especially when the gum changes are absent. The presence of a marked degree of pyrexia is in favor of periostitis, for in scurvy, fever is usually absent or trivial in amount. If the other signs of scurvy are present as well, the diagnosis is clear, but sometimes one may be obliged to fall back on the therapeutic test.

3. *Infantile Paralysis.*—When infantile paralysis sets in, as it sometimes does, with a marked degree of hyperesthesia, it may simulate scurvy. There is no swelling of the affected limb and the other signs of scurvy are absent.

4. *Epiphysitis.* Epiphysitis may simulate scurvy but the swelling in the latter extends along the shaft of the bone and is not confined to the neighborhood of the epiphysis.

5. The changes in the mouth may be mistaken for those of ordinary *ulcerative stomatitis.* In scurvy the changes are confined to the gums, while in stomatitis they extend to the lips and cheeks as well. The ulceration in the mouth which often occurs in *acute leukemia* may lead to a suspicion of scurvy. Here the examination of the blood will at once settle the diagnosis.

6. Cases with hemorrhage into the orbit may be mistaken for *sarcoma of the skull* or for *chloroma.* In the former there are usually signs of sarcoma elsewhere and in the latter the blood shows an excess of lymphocytes while in both the positive signs of scurvy are absent.

7. The *hematuria* of scurvy is apt to be mistaken for renal hemorrhage from other causes. In a doubtful case of bleeding from the kidney it is therefore always well to try the effect of an antiscorbutic diet before proceeding to other measures.

8. *Fracture of the femur* may simulate some of the appearances of scurvy but in a doubtful case a radiogram should obviate error.

Prognosis.—This is favorable, provided the disease is recognized in time and suitable treatment adopted. Nothing in therapeutics is more striking than the rapidity with which such patients improve under a change of diet, although some degree of thickening of the bones may persist for a long time. Death is usually the result of intercurrent diseases, of which bronchopneumonia and chronic diarrhœa are the most frequent, although sudden hemorrhage, cardiac failure, or exhaustion may occasionally lead to a fatal issue.

Treatment.—This consists solely in altering the diet. Tinned food and sterilized milk must be stopped at once, and the child put upon a due allowance of unboiled milk. Fruit juices should be added, four teaspoonfuls of grape or orange juice sweetened with a little sugar being given daily. Baked potato is also useful, a little of the part under the skin being rubbed up with the milk into a thin cream, which is either added to the bottle or given separately (two teaspoonfuls three or four times a day). Raw meat juice is of value, and may be given in quantities of half an ounce daily. Drugs are of no use except to meet special indications. During the period of convalescence cod-liver oil and iron are helpful.

Scorbutic infants should be handled carefully and the clothing should be so constructed that it can be easily taken off and on. If it is necessary to move the child about he should be placed on a pillow. The affected limb should be steadied by light splints or wrapped in wet towels, which, if allowed to dry in position, afford considerable support. In mild cases a casing of cotton wool secured by a light bandage is sufficient protection.

CHAPTER XXVIII

RICKETS

By GEORGE F. STILL, M.A., M.D., (Cantab.), F.R.C.P.

Up to recent times, certain conditions were included under the name of rickets which are now believed to be entirely distinct pathologically. The disease which is now called infantile scurvy (Barlow's disease) was formerly described as acute rickets, hemorrhagic rickets, or scurvy-rickets; and under the head of fetal rickets was classed the disease now known as achondroplasia. Rickets will be described here under three heads: (1) Congenital or fetal rickets, (2) ordinary rickets as seen in the first two or three years of life, and (3) late rickets. Congenital and late rickets are (in the opinion of most observers) extremely rare; moreover, there is still some doubt whether the conditions described by these names are in all cases identical pathologically with the common rickets of infancy. It will be convenient, therefore, to describe the common form of rickets first, for it is in this form that the characteristics of the disease have been most carefully observed.

Geographical Distribution.—There is a general consensus of opinion that rickets is more prevalent in temperate zones than in very hot or very cold countries, but this vague generalization rests on no firm basis. Rickets has a wide distribution in the northern hemisphere and, although figures are lacking for the southern hemisphere, the disease is known to be prevalent in Australia, South Africa, and South America. The geographical distribution is no doubt to some extent dependent upon differences in the amount and intensity of sunlight in different countries. It has been observed that in tropical zones the disease is less frequent and less severe than in temperate zones, and it has been specially noted that in tropical countries the poor who live much in the open air, that is in the sunlight, are less affected than the wealthier persons who live much indoors. Its infrequency at high altitudes is also perhaps due to the greater exposure to sunlight in such parts. It is generally held that rickets is a disease chiefly of cities and large towns and probably here also deficiency of sunlight is one factor, but social conditions, especially by their effect upon diet, are of more importance than geographical limits.

Season.—Rickets comes under observation more often in winter than in summer and it has been assumed that it begins more often in winter. Observers in New York state that in their experience 75 per cent. of cases of rickets begin in the first half, and 25 per cent. in the second half of the year (Hess). In other countries also, *e. g.*, in Vienna (Kassowitz, Harriette Chick and others) a special incidence during the winter has been noticed.[1]

[1] Harriette Chick and others: Studies of Rickets in Vienna, *Med. Research Council*, 1923 (Bibliography).

This is now attributed to lack of sunlight.[1] It has been correlated also with a seasonal variation in the amount of inorganic phosphate in the blood in infants, Inorganic phosphate is at its lowest in the blood during the dark winter months. Diminution of phosphates in the blood is one of the phenomena of rickets. The phosphates can be increased artificially by exposure to sunlight or to the rays of the carbon arc-lamp (Hess and Lunddagen[2]) so that the seasonal fall in the phosphates is reasonably attributed to deficiency of sunlight.

Age and Sex.—The onset is so insidious that any exact determination of the age at which it begins is usually impossible. It rarely begins after the age of three years, and probably seldom before the age of three months. Among hospital out-patients the second year of life shows the largest proportion. Out of 1662 cases of rickets, 1268 were between one and two years old (Comby). Some statistics of consecutive patients under the age of three years taken from the writer's out-patient clinic illustrate the relative frequency at various ages:

	Birth to 3 months.	Months 3–6.	Months 6–12.	Years 1–2.	Years 2–3.
Rickets	10	10	24	38	18
No rickets	31	24	22	27	20

Recent observations in Vienna (Harriette Chick, Margaret Hume and others) with diagnosis by roentgen-rays showed a larger proportion of cases in which the date of onset was within the first six months (10 out of 14 cases).

It seems probable that there is little, if any, relation to sex. Out of 179 female children in the hospital, 73, that is 40.8 per cent., showed rickets, and 57 of 138 boys, that is 41.3 per cent.

Etiology.—Since the days of Glisson, who in 1650 discussed the etiology of rickets, there has been constant questioning as to its cause. Recent research has thrown new light upon the subject but there is still much that is uncertain. Even the one fact that seemed established, that rickets is a diet disorder, has been disputed recently. Deficiency of sunlight has been regarded by some as a more essential factor than any diet deficiency, and even if diet deficiency is the chief cause, its exact nature is still in dispute. It will be convenient to consider first, the exciting causes in accordance with recent research, and then those more general contributory causes upon which there is a measure of agreement.

1. **Dietetic.**—The theory which arose out of the work of Gowland Hopkins, that vitamine deficiency is the sole cause of rickets has obtained a wide acceptance. Experiments (Mellanby) showed that by feeding puppies on a diet deficient in vitamine A (the so-called fat-soluble vitamine) a condition apparently identical with rickets could be induced. Experiments on rats (McCollum, Zilva and others) showed that their nutrition and growth were hindered in a remarkable way by deficiency of this kind, and that the morbid conditions induced could be cured rapidly by administration of substances rich in fat-soluble vitamine, such as cod-liver oil.

[1] Hess and Unger: *Am. Jour. Dis. Children*, 1921, **22**, 186.
[2] *Jour. Am. Med. Assn.*, 1922, **79**, 2210.

It has long been recognized that cod-liver oil and other fatty substances, *e. g.*, yolk of egg, are curative of rickets in children and the discovery that these are especially rich in the fat-soluble vitamine seemed to confirm, the view that deficiency of this particular vitamine in the diet is the cause of rickets in children.

What however was originally thought to be a single factor now proves to be more complex, and the so-called fat-soluble vitamine comprises at least two components, a growth-promoting factor and an antirachitic factor. Either of these may predominate and in this way a substance containing fat-soluble vitamine may have very little antirachitic value but very great growth-promoting value, or *vice versa*, or may be rich in both, *e. g.*, spinach is rich in the growth-promoting factor but shows no antirachitic value (Goldblat and Zilva[1]), cod-liver oil is rich in both; butter contains both only in moderate degree.

It is only recently that the differences in quantitative value as regards the antirachitic factor in different foods which contain fat-soluble A have been appreciated; the significance therefore of experiments and observations made a year or two ago may have to be revised. It seems to be proved that deficiency of a certain factor, the so-called antirachitic factor comprised in vitamine A plays an important part, probably the chief part, in the causation of rickets.

Recent experiments show that beside this vitamine deficiency, a deficiency absolute or relative of calcium and phosphorus in the diet favors the onset of rickets without apparently being essential to its production. Possibly children who develop rickets in spite of a diet which is not defective in calcium or phosphorus may be excreting an abnormally large proportion of their intake.

In what way the antirachitic factor acts is at present unknown, presumably it influences calcium metabolism but whether directly or indirectly remains to be proved.

The conclusions derived from biochemical research as to the importance of deficiency of the antirachitic factor of vitamine A in the causation of rickets must carry the more weight as they confirm and explain clinical facts which were pointed out at least thirty years ago by Cheadle, and later by the present writer and others, as to the part played by deficiency of fat in the production of rickets in children. These facts are (1) that the diets upon which rickets most often arises, have for the most part one feature in common, namely, deficiency of fat, (2) that the treatment which has been recognized in England for at least fifty years as the most effective for the cure of rickets is administration of cod-liver oil, while for its prevention, milk, yolk of egg, and cod-liver oil have also been long recognized as specially valuable. Similar facts were ascertained by Bland-Sutton nearly forty years ago with reference to young monkeys, bears and lions in the Zoölogical Gardens in London.

Apparent exceptions were observed, and were difficult to understand so long as it was supposed that all fats were of equal value in the prevention of rickets and that milk, whether human or bovine, must always be

[1] *Lancet*, 1923, ii, 647.

of equal antirachitic value, but with the advent of the vitamine theory some at least of these supposed exceptions have been explained, for we now know that a milk may be very deficient in fat-soluble vitamine if the intake of that vitamine in the food has been deficient; for a mother, whether human or bovine, is not a maker but only a purveyor of vitamine. Fats whether animal or vegetable are not all rich in fat-soluble vitamine. Some indeed, especially those of vegetable origin, are almost devoid of this vitamine, so that a child might be having a diet rich in fat and yet become rickety.

Deficiency of the antirachitic factor may not *per se* induce the typical changes of rickets. The age incidence of rickets suggests that a certain degree of activity of growth is one of the conditions determining these changes. Experimental and clinical observations seem to show that if growth is arrested, or proceeding but slowly, as happens if the growth-promoting factor is deficient, then deficiency of the antirachitic factor may produce softening of bone without the characteristic epiphyseal changes of rickets.

2. **Contributory Causes: Defective Hygiene.**—Rickets is more frequent in cities than in country districts and this has suggested that defective hygiene is responsible for the disease. In many of the cities where rickets is most prevalent there is much overcrowding, and where a whole family of several children with their parents live in one room, the vitiated atmosphere may well interfere with the nutrition of an infant who spends the greater part of the day and night in this one room. Undoubtedly in London rickets is far commoner among the poorer classes than among the wealthy; but it seems likely that the difference lies much less in environment than in feeding. The children of the well-to-do become rickety when fed in the same way as the children of the poor. The minor part played by environment seems to be shown also by the fact that, in London at any rate, rickets is usually treated among hospital patients by simple dietetic measures and the administration of cod-liver oil, with no change of environment; and yet the results of such treatment are excellent. The same objections might be urged against the view that deficiency of sunlight is a large factor in the causation. In cities, with narrow streets and high buildings, the rooms of the poor are often ill-lighted and get little or no sunshine. But it is equally true that in some less-civilized parts of the world, where rickets is said to be extremely rare, it is customary to live in dwellings even less open to sunlight.

If, however, there is little evidence that overcrowding and squalor have much influence *per se* in the production of rickets, clinical experience seems to indicate strongly that certain conditions of city and town life do play a very important part. The struggle for existence in these crowded districts often makes it necessary that both parents should go out to work, and infants are therefore artificially fed; moreover, wherever poverty abounds, the cheaper substitutes for cow's milk are likely to be used, especially condensed milk. It seems probable also that, particularly among town-bred women, there is an increasing inability to suckle their offspring, which favors the occurrence of rickets.

Parental Influence.—Direct heredity has been held accountable by some (Henoch, Pfeiffer, Ritter von Rittershain). Ritter found traces of rickets in the mothers of 27 out of 71 rickety children. But in the districts from which observations on this point have come, rickets is a common disease, and it is at least possible that parent and child have both been subjected in early life to faulty methods of feeding. The health of the mother during pregnancy has long been considered to have some influence upon the development of rickets in postnatal life. Phthisis during pregnancy was especially mentioned by Garrod and Fletcher[1] as a cause of rickets in the offspring, and the same writers consider that want of fresh air and exercise during pregnancy has a similar results; they mention, also, multiple pregnancy, and pregnancy at an advanced age, or at an unduly early age, as factors.

It is commonly stated that the last children born in a large family are more often affected with rickets than the earlier children, especially if the pregnancies have been not only numerous but in rapid succession. In such cases it is supposed that exhaustion of the mother interferes with the nutrition of the infant so that rickets appears after birth. Similar in its effect, presumably, is lactation during pregnancy, which some observers have thought to be a cause of rickets in the offspring.

Whether any of these influences can be regarded as more than predisposing, is doubtful. Rickets at birth is generally thought to be exceedingly rare, and when the disease makes its appearance some months after birth, there is always a possibility and often a probability that postnatal factors, particularly the feeding, played a larger part in producing the disease than any parental influence before birth.

Syphilis.—Parrot's view that syphilis causes rickets is now discredited; but some still hold that syphilis strongly predisposes to rickets. Undoubtedly, some of the most severe degrees of rickets are seen when this disease is associated with congenital syphilis, and it would seem that in such cases the osseous and perhaps the visceral lesions of rickets may be modified not only in degree but also in kind. In the skull, osteophytic change is more common and more marked when syphilis is associated, it may occur with rickets alone. Some have thought also that localized thinning of the cranial bones, craniotabes, is especially frequent when these two diseases are combined.

Pathology.—Morbid Anatomy.—The most obvious change is the enlargement at the junction of epiphysis and diaphysis in the ribs and in the long bones. This is due to change in the two transverse zones at the junction of the epiphysis and diaphysis in a growing bone, the so-called "zone of proliferation" and the "zone of calcification." The bluish-gray zone of proliferation is enlarged so that it may be more than twice the normal thickness, and instead of being an even band with sharply defined edges limiting it from the cartilage on the one side and the zone of calcification on the other, it is quite irregular, especially toward the zone of calcification, where, even with the naked eye, it can be seen that the two zones are mixed together, islets of calcifica-

[1] *Brit. Med. Jour.*, September 21, 1895.

tion are seen amidst translucent cartilage, and irregular processes of cartilage extending into the region of calcification, and the whole is abnormally vascular, so that to the naked eye, numerous vessels are obvious, traversing these confused zones in all directions.

Histologically, there is the same confusion; the cartilage cells are more numerous than they should be, the arrangement of columns has lost its regularity; they are ill-formed and no longer parallel. Between them in many places are areas of calcification, sometimes even of fully formed laminated bone, lying amid cartilage cells and cartilaginous matrix in which are numerous vessels passing inward from the adjacent periosteum or perichondrium. The cancellous tissue of the shaft has also an undue vascularity, and the absorption of this tissue which should proceed but slowly, keeping pace with the formation of new bone from the periosteum without, proceeds in rickets too rapidly, so that the bone consisting of an imperfectly ossified layer without, is further weakened by the rarefaction and looseness of its cancellous tissue within.

The subperiosteal formation of bone is also disturbed, the periosteum itself becomes thickened and the proliferating layer beneath, in which calcification should occur, is excessively vascular, and contains abundant cell elements, but is imperfectly calcified, and the production of true laminated bone is deficient, so that the bone here also is softer than normal and bending easily occurs. The bone thus formed may be of spongy character, a condition especially noticeable in the thickened area of the parietal and frontal bones, where also the vascularity is sometimes so great that it can be observed clinically as a bluish discoloration seen through the tense scalp.

Characteristic changes at the *epiphyseal junctions*, and sometimes also in the subperiosteal region, are shown by roentgen-rays. The lower radial and ulnar epiphyses are convenient for the study of these changes. In an early stage there is a cup-like expansion of the lower end of the diaphysis which, instead of appearing as a clean-cut straight line, has a more or less crescentic curve (Fig. 100) and a more ill-defined margin than normal. In a more advanced stage the irregularity has become more obvious so that the end of the diaphysis looks like the pile of velvet or almost brush-like, owing to irregular streaks or spicules of ossification. In a still more advanced stage (Fig. 101) the irregularity is such that the line has lost its linear character altogether and the lower end of the diaphysis has a jagged uneven margin in which bays of translucent cartilage are mixed up with islands or promontories of darker calcified bone. Sometimes, as in the roentgenogram shown here, fractures and bending of the bone give still further evidence of rickets.

Muscles.—It is stated that the muscles show microscopically some blurring of striation, and that there is excess of fat in the connective tissue between the muscle fibres. In severe cases, fatty degeneration of the muscle fibres themselves has been observed.

Viscera.—The liver is sometimes enlarged, and the spleen also to a slight degree. In both some observers have found slight increase of fibrous stroma, but the relation of this to the rickets is uncertain. The lungs show no characteristic change.

Pathogeny.—Chemistry of Rickets.—The vitamine deficiency theory of rickets has placed the chemistry of the disease in a new perspective. Formerly the primary cause was sought in some purely chemical fault, and as calcium and phosphorus are the chief constituents of bone, it was supposed that deficiency of these whether by failure of absorption from the food or by deficient intake, or some disturbance of their relative proportions in the diet was the natural explanation of rickets, in which

Fig. 100.

Fig. 101.

defective growth and calcification of bone are conspicuous features. It was pointed out, however, that the facts to be explained are not merely the softening and bending of bone but the overgrowth of cartilage, the perversion of the whole process of bone formation and in addition more general disturbance especially in the nervous system, and also in the muscles and viscera. There is evidently some wide disturbance of metabolism.

Several observers found that by feeding animals on food deficient in

lime they could induce softening and bending or fragility of bones, but the characteristic features of rickets, the overgrowth of cartilage and perversion of the process of bone formation as seen at the epiphyseal lines, were lacking. It was felt that no mere chemical formula would explain a condition so intimately bound up with biological processes. Some factor was needed which could link up the chemical changes with the disturbances of vital phenomena which are so conspicuous in rickets and this factor is probably to be found in deficiency of that constituent of vitamine A which has been called "the antirachitic factor." At present, therefore, as a working hypothesis it may be assumed that while deficiency of calcium, or of phosphorus, or of both, or perhaps a disturbance in their relative proportions, whether produced by faulty diet or by failure of absorption, is a contributing cause, this can only produce rickets when there is with it deficiency of the "antirachitic factor" of the fat-soluble vitamine A.

Whether deficient intake or absorption of calcium or phosphorus is essential or whether deficiency of the "antirachitic factor" by itself can cause rickets is still in dispute. Some experiments by Shipley and Park seemed to show that, if the phosphorus level was maintained, deficiency of the fat-soluble vitamine did not cause rickets, whereas a normal calcium level in the serum of rickety children was found (Howland and Kramer) to be quite consistent, indeed a common occurrence, with rickets so that it would seem that phosphorus deficiency is a more important factor in the etiology than deficiency of calcium. Nearly 90 per cent. of the salts of normal bone consists of tricalcium phosphate and any considerable disturbance of the ratio of calcium and phosphorus in the blood might be expected to disturb bone formation.

The observations made by Freund on the part played by fat in the diet in promoting the absorption of phosphates have been supported by more recent research (Telfer). It is probable therefore that apart from the fat-soluble vitamine, fats may have an important influence in preventing or curing rickets. It has been found that cod-liver oil causes the phosphorus in the blood, if deficient, to rise to normal (Howland and Kramer).

Bacteriology.—Experiments with injection of organisms and with pieces of bone and feces from rachitic infants have failed to produce the disease. There is no proof that rickets is caused by bacterial infection.

Symptoms.—Rickets is a disorder of nutrition, and, as such, affects the whole organism. The bone changes are only part of a general disease. Much of the confusion as to the pathogeny and even the diagnosis has resulted from the tendency to concentrate attention upon the osseous lesions to the exclusion of other features. A child may suffer severely and yet show so slight a degree of rachitic change in the bones that the disease might almost pass unnoticed if only the osseous system were considered. The stress may fall upon the nervous system in one case, upon the muscular in another, and perhaps even upon the blood and blood-forming tissues in a third.

Before describing the symptoms in detail, an outline of a typical and well-marked case of rickets may be given. An infant, aged about eighteen months, is brought for inability to walk. He has been suckled entirely perhaps for six or seven months, and then has had condensed milk and

occasionally bread or potato. For some months past, he has sweated profusely about the head and neck whenever he falls asleep. Dentition did not begin until he was nearly a year old, and even now he has but three or four teeth. He has never walked, and as he sits on his mother's lap there is a marked kyphosis especially in the upper lumbar region. He is pale and fretful; perhaps rather fat, but flabby; the head is unduly large, with a tendency to squareness; the anterior fontanelle is much more widely open than it should be at this age. The chest is ill shaped, the sternum a little prominent, and there is some transverse constriction below the level of the nipples. A row of knob-like eminences marks the junctions of the costal cartilages with the ribs on each side of the chest; the lower ribs are somewhat everted above the big abdomen, in which the liver can easily be felt, and the spleen is also just palpable. The muscles feel flabby and soft. Just above the ankle and the wrist, the bones seem thickened. There is little or no abnormal curvature of the bones.

Such is a moderate degree of rickets; but there are many more in which the symptoms are altogether less marked, and perhaps delay of dentition and of closure of the fontanelle, with slight thickening at the costo-chondral junctions (beading of the ribs), and possibly, but not necessarily, some enlargement of the radial epiphyses, are the only evidences of the disease. There are also cases, much less frequent, in which the symptoms are altogether more severe, the limbs are deformed by bendings and distortions of the bones, the cranium is irregularly thickened or thinned, and the child perhaps shows severe nervous symptoms, convulsions, or laryngismus stridulus.

Nutrition.—The child is often unduly fat, especially in slight, or moderate degrees of rickets. This deposit of fat is apparently derived from carbohydrate food, for it is seen when the diet is greatly deficient in fat. It would seem that this stored fat is unable to replace the functions of fat taken as such in the food. In severe rickets wasting of greater or less degree is common.

Head Sweating.—This is often one of the earliest symptoms and may be so profuse that the pillow is soaked. It usually occurs when the child falls asleep; it is not present in all cases. Probably with this is associated a feeling of heat, for the infant at this stage is very apt to push the bedclothes off at night and lie uncovered.

Temperature.—This is normal in most cases even during the most active stage, so far as the writer's observations go; a rise of temperature is almost always due to some complication.

Teeth.—Delayed dentition is one of the most constant symptoms. In 32 out of 42 consecutive cases, between nine months and three years old, this was present. Frequently no teeth have appeared at the end of the first year. Rarely their appearance is delayed beyond the age of eighteen months. There is a striking tendency to very early caries; even before the tooth is fully cut the enamel at the cutting edge is often completely destroyed. If dentition has begun before the onset, it is often arrested for several months.

Muscular Weakness: Laxity of Ligaments.—Muscular weakness is very common in the active stage, and in the more severe cases is almost always well marked. It may be quite out of proportion to the osseous changes, and for this reason is liable to be mistaken for some paralysis of nervous origin; it may be so great that a child of two or three years is unable to stand or even to sit up. The late acquirement of sitting, standing, and walking is chiefly due to this weakness, though in part, no doubt, to laxity of ligaments, and to bone changes. The child who has already begun to stand often loses this power at the onset. The stooping of the back, or kyphosis, which is common in rachitic children, would seem to depend chiefly upon weakness of the muscles of the back. It is possible that muscular weakness of the respiratory muscles plays some part in the tendency to pulmonary affections.

The effects of muscular weakness are intensified by laxity of the ligaments, apparently from some structural change which renders them soft and yielding. The child can often place his toes behind the ears without difficulty; and the head of the tibia shows an undue amount of lateral mobility, so that it can be loosely knocked against the condyles of the femur. Both these changes, the muscular and the ligamentous, contribute to some of the deformities, such as talipes valgus and planus, genu valgum and varum, and lateral curvature of the spine.

Osseous Changes.—These are the outcome of the delayed and imperfect ossification, hyperplasia, and abnormal absorption of bone tissue. The most frequent manifestation is the so-called "rickety rosary," or beading of the ribs, a thickening at the costo-chondral junction which in a thin child can be seen and in others easily felt. These beads are usually largest and most readily felt on the fifth, sixth and seventh ribs, and in a mild case may be scarcely perceptible on other ribs. They are often seen post-mortem to be more marked on the internal than on the external surface of the thorax. The internal bead, however, is sometimes exaggerated by a displacement of the bony rib backward at the costo-chondral junction, so that, instead of joining the cartilage end to end, it joins it at an angle which projects on the inner aspect of the thorax (Fig. 102). In such cases the external beading may be obscured altogether, and the junction of rib and cartilage forms a depression externally, so that, clinically, beading may not be detected. The rickety rosary is one of the earliest symptoms and is often the only bone change to be found during life. It gradually diminishes after the fourth and fifth year and has usually disappeared before puberty.

As a result of the backward displacement of the anterior portion of the rib, in some cases there is an exaggeration of the angle of the rib, posteriorly, or actually a green-stick fracture at that situation; the projections formed thus are sometimes described as "posterior beading," but are obviously different in their pathology from the anterior "rickety rosary."

Enlargement of *epiphyses* is very common and generally most marked at the lower end of the radius, where some thickening was present in 64 per cent. of the writer's cases. At the lower end of the femur and tibia it is also frequent. Other long bones show it less frequently. The ends of the phalanges of the fingers are occasionally affected, giving a somewhat

spindle-shaped appearance. Some thickening of the diaphysis of the phalanges has also been described (Koplik).

Owing to the softness of the bones, some degree of curvature in the limbs is common; 43 per cent. of the writer's patients showed curvature of the bones either in the upper or in the lower limbs, but in most of these the bending was slight in degree. The commonest deformity of this kind is a bending outward of the lower third of the tibia—sometimes there is combined with this, or alone, a forward bend which may be slight or may be sharply angular in the lower third (Fig. 103).

The femur is less often affected; it shows a general outward curve in children who are already able to stand or walk when the rickets affects them. In children who are carried about on the nurse's arm, the curve in the femur is often antero-posterior with the convexity forward. A much rarer result is the condition known as "*coxa vara*," in which the head of the femur is bent downward so that it is at the same level with, or even lower than, the great trochanter, while the neck of the femur is curved with the convexity forward and upward. Bending of the bones of the upper limbs takes place chiefly in children who spend much of their time crawling about or in the sitting position supporting the weight of the trunk partly upon the hands; a favorite position is that shown in the illustration (Fig. 104), where the child sits tailor-wise and uses its hands as a prop. Both the humerus and the bones of the forearm are usually curved outward in such cases. The clavicle, in severe cases, often shows a sharp angular bend forward and upward at the junction of the inner and middle third; and sometimes there is evident thickening here, the result of a green-stick fracture.

Fig. 103.

Photograph of a cast at the museum of the Hospital for Sick Children, Great Ormond Street, London, showing a common rachitic curvature of tibia.

Fig. 102.

Antero-posterior section of costo-chondral junction to show rachitic displacement. In the upper specimen the displacement is slight, in the lower there is complete displacement.

All these deformities are the result partly of pressure from without, partly of the weight of the body, and partly of muscular traction upon the softened bones.

Similar in their production are the rachitic deformities of the *thorax* and *pelvis*. The former shows a lateral contraction so that the sternum and costal cartilage appear to project forward in front of the ribs, while the depression at the junction of each rib and cartilage forms a furrow passing downward and outward and usually lost in a deeper transverse groove just below the level of the nipple, the so-called "Harrison's sulcus."

FIG. 104.

Common position of rickety child with bending of forearm, showing also large head, large abdomen, and deformed thorax with Harrison's sulcus.

This sulcus, which extends from the ensiform cartilage to the posterior axillary line, is commonly associated with eversion of the lower ribs over a distended abdomen which increases the distorted appearance of the chest. The pigeon chest (*pectus carinatum*), in which the ribs appear straightened as they pass from the posterior axilla to join the prominent sternum so that the cross-section of the thorax would be roughly triangular with the apex at the sternum, is often described among rachitic deformities. Neither pigeon chest nor "Harrison's sulcus" are essentially rachitic. They are seen in any condition in which there is obstructed respiration.

Pelvic deformities hardly enter into the clinical picture of rickets in childhood, for they attract no attention at that age, although in the

adult female they become of great importance. Rickets here, as in the rest of the bones, may arrest development, so that the pelvis remains small and generally contracted. Often there is in addition flattening of the pelvis antero-posteriorly; it is shallow, and, occasionally, from traction of the muscles and the pressure transmitted from the spine and from the femora, more marked distortion takes place.

The bones in rickets become not only soft but brittle, so that fractures, usually of green-stick character, are apt to occur in severe cases with little evidence of traumatism, sometimes apparently from muscular traction alone. This tendency depends partly on absorption of cancellous tissue in the rickety bone, partly on deficient calcification, and partly perhaps upon some abnormal arrangement of the trabeculæ.

As a result of the epiphyseal affection and of the sclerosis which may occur in the bones after the rachitic process has ceased to be active, permanent stunting of growth occasionally takes place, so that the child may be undergrown or actually dwarfed for the rest of its life.

Cranium.—One of the most constant symptoms is delay in the closure of the anterior fontanelle. Normally this should measure about ¾ to 1 inch (2 to 2.5 cm.) antero-posteriorly and transversely at the end of the first year and should close at or about the age of eighteen months. In rickets, it often measures 2 inches (5 cm.) in both directions at twelve months, and is frequently open as late as two and a half or three years; the writer found it open at four and a half years. This delay of closure is not due to any general expansion of the skull such as occurs in hydrocephalus, for it occurs equally where there is no enlargement of the head and where the head is, as often happens in rickets, unduly large; it indicates rather a general backwardness in bone formation which may determine more extensive failure of consolidation so that the interparietal and the parieto-occipital sutures are not firmly united for many months.

The size of the head is commonly above the normal; in 17 cases of rickets with an average age of 4.72 years, Lucas[1] found that the average circumference was 21.2 inches (54 cm.), whereas in 17 non-rachitic children with an average age of 6.05 years, the average circumference was 19.95 inches (50.5 cm.). The cause of this increase in size is uncertain; sometimes the brain has been found above the average weight and in some cases there is considerable thickening of the bones of the skull, though hardly sufficient to account for the large size. The rachitic skull differs from the normal not only in size but also in shape. Two types may be recognized. In the one, the more frequent, the skull is flattened on the vertex and tending to squareness; the posterior segment especially is enlarged; in the other the head is narrow from side to side and elongated antero-posteriorly. The softening of the bones is shown in the skull by the deep grooves which are hollowed out on its surface by the veins of the scalp so that their course can easily be traced by running one's finger-nail along the groove.

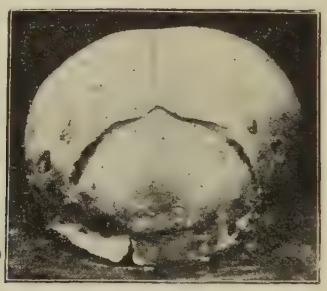
The relation of bossing of the skull and of craniotabes to rickets has been much disputed. Both have been attributed to syphilis by some, and to rickets by others. So far as personal observations go, both seem

[1] *Pathological Society Transactions*, vol. **32**, 359.

to occur in rickets apart from syphilis but to be aggravated when syphilis is added to rickets. Some have thought that the symmetrical bosses which occur on the frontal and parietal bones, giving rise to the "*caput quadratum*" or "*hot-cross-bun head*," can be distinguished by their position from those of syphilis, which are said to be closer to the anterior fontanelle. However this may be, there are certainly two conditions, very different in appearance, which give rise to the local thickenings felt on the skull. In the one, the surface of the bone is smooth and the thickening is due to a very vascular increase of the cancellous tissue between the compact inner and outer tables; in the other, there is a deposit of vascular spongy bone on the outer surface of the skull, which has a roughened, worm-eaten appearance. Whether these represent different stages of one and the same process or whether they indicate different processes is at present uncertain.

The term "*craniotabes*" is used with varying significance. Some would apply it to a diffuse yielding of bone near the suture, especially about the parieto-occipital sutures, which is not uncommon in rachitic

FIG. 105.



Posterior view of rachitic skull, showing characteristic areas of true craniotabes.

children under twelve months of age and is exceedingly common in infants during the first two months of life. In early infancy this thinness of the bone is often associated with unusual separation of sutures and patency of the fontanelles, posterior and lateral as well as anterior. It is very doubtful whether such a condition should be taken as necessarily indicating rickets; certainly it is quite common during the first three or four months of life in breast-fed infants, particularly those of small size and feeble development, with no other evidence of rickets.

Much more significant are localized patches of thinning of the bone situated generally in the occipital or in the parietal bone (more commonly the latter) near to, but not actually adjoining, the parieto-occipital suture, from which they are separated by an area of firm bone (Fig. 105). The patches are usually about $\frac{1}{2}$ to 1 inch (1.5 to 2.5 cm.) in diameter, round or oval, and can be detected by taking the head between the palms of the hands so that the fingers rest on the posterior parietal and occipital region. On pressing firmly with the fingers, the affected areas are felt to yield, bulging inward like a piece of thick parchment and rebounding when

pressure is removed. In severe cases these areas run together, but even then the irregular and patchy distribution distinguishes them usually from the diffuse thinness mentioned above. This condition, unlike the diffuse thinness of the edge of the bone, is often found when the sutures are well closed and only the anterior fontanelle remains patent. It occurs often in the second year of life in children who have only developed rickets after the skull bones are already well ossified. It is an absorption of already formed bone, not a mere delay of development as the diffuse thinness with patent sutures probable is in some cases.

According to the meaning attached to craniotabes, its frequency has varied in statistics. According to observations made by S. Fraser upon children under three years of age at the Children's Hospital, Great Ormond Street, London, 29 per cent. of the rickety children showed craniotabes, but this series included many cases in which there was only yielding of the bones near the sutures.

There can be no doubt that craniotabes occurs with rickets without syphilis. In the form of isolated patches it is associated particularly with laryngismus stridulus and tetany, the former of which, if not also the latter, when it occurs in childhood, occurs almost exclusively in the rachitic and has no connection with syphilis. Out of 21 cases of laryngismus stridulus in which the writer noted this point, craniotabes was present in 7. According to Barlow and Lees, 47 per cent. of cases of craniotabes show evidence of syphilis; but many of their cases with syphilis had rickets.

Nervous Symptoms.—*Mental.*— The rickety infant is often fretful and peevish, but perhaps more from the discomfort of prolonged ill-feeding than from any direct effect of the disease. In later childhood, rickets has been described as a cause of precocity, and the large head has been supposed to allow a larger capacity for mental development. Thackeray has been quoted as an instance. The accuracy of these observations is questionable; the child invalided by any chronic disease is likely to be much with its elders and to acquire a precocious manner. The writer is unable from his own observation to affirm any intellectual superiority in rachitic children. There is no evidence that they are inferior, although it was stated by Sir W. Jenner that "Children the subjects of extreme rickets are almost always deficient in intellectual capacity and power."

Convulsive conditions are the chief evidence of rickets affecting the nervous system: from about the sixth to the twenty-fourth month convulsions in infancy are most often due to it. The cortex is in some way rendered so unstable that trivial exciting causes, such as constipation or dentition, are sufficient to induce an attack. As part of this convulsive tendency must be reckoned laryngismus stridulus and tetany with their almost constant accompaniment—the so-called "facial irritability."

In *laryngismus stridulus*, a spasm of the larynx suddenly closes the glottis so that the infant is for a few seconds unable to draw air into the chest: the face becomes livid, the infant looks terrified, and makes violent efforts to inspire. After a few seconds the spasm relaxes and a deep inspiration is taken with a loud crowing noise. These attacks come on usually when the infant begins to cry or just as it wakes, or a sudden

draught of cold air may start them. There may be many in the day or only two or three in a week. If the spasm is prolonged many seconds, the infant becomes cyanosed and may pass into a general convulsion or die silently of asphyxia. These attacks occur most often between the ages of six and eighteen months; they are rare after the age of two years. Of 35 cases, 32 showed definite rickets, 2 probable rickets; only 1 showed no bone manifestations of rickets.

Tetany, a tonic spasm affecting chiefly the muscles of the forearm and hand, and leg and foot, is in young children almost always associated with rickets. The hand is generally slightly flexed at the wrist, the thumb is adducted so that its tip points to the interval between the ring and the mid-finger, the rest of the fingers are semiflexed at the metacarpo-phalangeal and extended at the phalangeal joints, often with some tendency to overextension at these latter. The toes are crowded together in a position so far as possible resembling that of the fingers; the foot is sometimes extended at the ankle. Apparently from some pressure on the veins by the contracting muscles, œdema of the hands and feet is often seen with tetany. The spasm of tetany is in some cases persistent for several hours or even for days; in others it is intermittent, lasting only a few minutes at a time and causing some cramp-like pain each time it recurs. It is most frequent at the age at which laryngismus stridulus is common, and is usually associated therewith.

A latent form of tetany is not uncommon in rickety children; it is demonstrated by the method described by Trousseau; the upper arm is firmly grasped so as to compress the vessels and nerves on the inner side of the arm, and after a period of thirty seconds to about two minutes, the hand assumes the characteristic position of tetany.

Of 24 cases of tetany in young children, 22 showed definite rickets, 1 doubtful rickets, and 1 no bone manifestations of rickets. Twenty-three of these cases were associated with laryngismus stridulus.

Facial irritability, Chvostek's sign, is also closely related to the convulsive manifestations of rickets. On gentle tapping over superficial branches of motor nerves, a contraction of the corresponding muscles occurs. This was first described with regard to the face, but is to be seen in the limbs also. Of 35 cases of laryngismus stridulus, 33 showed this nerve irritability; and it is almost always present with tetany whether this is associated with laryngismus stridulus or not. Facial irritability is found in rickets also apart from laryngismus stridulus and tetany, and is then probably always an indication of a convulsive tendency. In some of these cases there is a history of preceding convulsions; in others, after the facial irritability has been observed, convulsions occur. It is therefore of value as indicating the need for such drugs as bromides, by which convulsions may be averted. This nerve irritability is probably most common in the face, but as the writer has notes of cases in which it was in the limbs only, the term facial irritability is not sufficiently inclusive.

Head nodding with nystagmus (*spasmus nutans*) needs only to be mentioned here, for, although it is generally associated with rickets (Hadden, J. Thomson), the rickets is regarded only as a predisposing cause. The pronounced nervous instability may show itself in other ways

—a rhythmic head-rolling upon the pillow so that the back of the head is rubbed almost bald, or head banging in which the child beats its head with its hands or against any object near, are both seen most often in rickety children, although the determining cause may be some peripheral irritation, dentition, or middle-ear catarrh.

Hydrocephalus was regarded by Jenner as sometimes produced by rickets but this view is now generally discarded. The large head of rickets, especially when the square shape is less pronounced than usual, may simulate hydrocephalus, but is probably rarely, if ever, due to distention of the ventricles.

The association of zonular or lamellar cataract with rickets, and especially with convulsions, has been noted by other observers since Davidson and Horner of Zurich drew attention to it in 1865.

Tenderness.—It is generally, stated that there is some tenderness present not only in the bones but also in the muscles (Gee). Hilton Fagge described this as one of the characteristic features. If such a condition occurs at all, it must be quite exceptional. The rickety child is often fretful and nervous, resents, or is frightened, by any examination; but if there is definite tenderness, the presence of scurvy with the rickets should be suspected.

Gastro-intestinal Symptoms.—The abdomen is usually distended so that the rachitic "pot-belly" has become a recognized term. The distention is due to three causes: flatulence arising from improper feeding; displacement downward of the liver and spleen by eversion of the lower ribs; diminished space in the small pelvis; probably to these may be added relaxation of the abdominal muscles so that they afford less support than normal. As a result of this distention, the recti muscles are often separated so that there may be a gap of 1 inch (2.5 cm.) between them; but this is not peculiar to rickets; it occurs in young children with chronic distention of the abdomen from any cause. In the gastro-intestinal, as in the pulmonary mucosa, there is a special tendency to catarrh.

The liver is often to be felt 1 inch (2.5 cm.) or more below the costal margin, but this is due in many cases, partly at least, to displacement downward by eversion of the ribs. The spleen, for the same reason, is often felt $\frac{1}{2}$ to 1 inch (1.5 to 2.5 cm.) below the costal margin; it is probably but seldom enlarged to any considerable extent, unless splenic anemia is to be regarded as a manifestation of rickets.

Respiratory System.—Bronchitis is very frequent in rachitic children and this tendency is favored, in severe cases, by the softness of the ribs and the weakness of the respiratory muscles. There is, in fact, a vicious circle. For the mechanical reasons mentioned, the lung is very imperfectly filled with air and the collapse thus induced favors the occurrence of bronchitis and hence further collapse. The movements of the diaphragm must be rendered less extensive by the eversion of the lower ribs and hampered by the abdominal distension.

Circulatory Symptoms.—Anemia is common and sometimes very profound. In severe cases the child may have a waxy complexion not unlike that of chlorosis, and Hutchison has referred to cases in which the blood changes corresponded. In a rickety infant, aged one year

and seven months, the blood showed four million red corpuscles and only 20 per cent. hemoglobin. The leukocyte count shows nothing characteristic; some observations by Thursfield and Drysdale[1] gave the following results: Hemoglobin, 44 per cent.; red corpuscles, 4,364,000; white corpuscles, 11,000; polymorphonuclears, 49.2 per cent.; lymphocytes, 46.8 per cent.; large mononuclears, 3.3 per cent.; eosinophiles, 0.5 per cent.; myelocytes, 0; occasional nucleated red corpuscles. This agrees very nearly with the average proportions of the differential count for a healthy infant of about twelve months, except perhaps for a very slight increase of polymorphonuclear cells.

A systolic bruit is frequently heard over the open anterior fontanelle,[2] and was formerly thought to be of value in the diagnosis between a rachitic and a hydrocephalic head (Rilliet and Barthez). It is, however as Osler showed, frequent in infants and young children who are free from rickets; it is most common in the second year of life but may be heard as late as the sixth year.

Complications.—Bronchitis is extremely frequent; bronchopneumonia is also common and is one of the chief sources of danger to life, especially where there is much rachitic deformity of the chest. Gastro-intestinal catarrh and diarrhœa are common and considerable dilatation of the stomach is sometimes evident both clinically and postmortem. Infantile scurvy is an occasional complication, but the association is to be regarded as a coincidence; there is no essential connection.

Diagnosis.—The clinical picture of severe rickets is so striking that it can hardly be mistaken. The projecting rickety rosary, the large epiphyses, the large square head, the bent limbs, are characteristic enough; but in slight cases the difficulty is greater and it is clear from a comparison of various observers' statistics that there is no general agreement as to what constitutes clinical evidence of rickets. For instance, in Munich at the same institution one observer found about 70 per cent. of the children under two years to be rickety; another observer found that less than 5 per cent. of the children were rachitic.

The most reliable criterion of rickets during life is the appearance, as seen in skiagrams, at the epiphyseal junctions. For this purpose the radial epiphyses are most convenient for observation.

Beading of the ribs has often been accepted as evidence of rickets, but this is not necessarily so; it is common to find beading of the ribs in healthy infants just after birth, and Escher found on microscopic examination that these showed none of the characteristic changes of rickets. Yielding of the skull bones on pressure, a diffuse thinness along the edge of the bones with some separation of sutures, has been taken as a proof of rickets, but this also is incorrect. A simple delay of development occurs quite apart from rickets and Fede and Finizzio concluded from a microscopic examination of the skull bones that the yielding of the skull in new-born infants was not necessarily due to rachitic change.

It seems probable that there are other bone diseases which may cause softening of bones or deficiency of calcification, so that bending or frac-

[1] *Med.-Chir. Society Transactions*, 1904.
[2] Still: *Brit. Jour. Dis. Child.*, 1921, **18**, 173.

ture of bones results. *Osteomalacia*, or mollities ossium, in which at an age usually beyond puberty the bones show progressive softening so that they bend in all directions, has been regarded hitherto as quite distinct from rickets in its pathology, recently however this view has been questioned. Occasionally cases are seen in childhood with extreme softening and bending of bones and lacking the usual characteristics of rickets, such as the enlarged epiphyses and the large square head. It may be that in some cases a condition like the osteoporosis produced experimentally in puppies occurs in children also and especially at an age when growth is only slightly active or has ceased altogether.

The weakness of the limbs may be mistaken for *infantile paralysis;* the general distribution, the gradual onset, the retention of reflexes and the changes in the bones will usually suffice for the distinction.

The kyphosis may be so marked as to suggest *spinal caries*; it is generally taught that the curve of rickets disappears when the child is held up supported under the armpits, whereas that of spinal caries remains. In long-standing cases, however, the kyphosis may not disappear thus, nor even when the child is made to lie on its face, and the diagnosis has to be made from the more general curving of the spine and from the signs of marked rickets elsewhere.

The enlargement of the head is sometimes difficult to distinguish from that due to *hydrocephalus*. As a rule the flattening of the vertex and the square shape distinguish the rachitic head from the more globular hydrocephalic head; but there are cases in which, if the child is first seen after the fontanelle and sutures have closed, the diagnosis may be impossible; and it is only when symptoms result from increasing tension in the ventricles that the question may be settled.

Course and Prognosis.—Rickets is readily amenable to treatment, and when once the disease has stopped, any recrudescence is very exceptional. Probably, some of the cases described as late rickets are of this nature. The intensity and duration of the symptoms vary chiefly according to the feeding; no doubt, in some cases as the child grows older and takes a more varied diet, which includes a sufficient proportion of the requisite constituents, the disease comes to a standstill without special treatment. In others it progresses so rapidly that within a few months considerable softening and bending of bones occurs, nervous and respiratory symptoms become pronounced, and the child dies. When death results from rickets, the immediate cause is usually bronchitis or bronchopneumonia, convulsions, or laryngismus stridulus.

Rickets is seldom seen in active progress after the age of three years, but the deformities may last for life. In their slighter degree some of these may disappear; the beading of the ribs is gradually lost in many cases and even considerable deformity of the chest may diminish greatly as the child becomes stronger and expands his lungs more thoroughly. Slight curvature of the legs may right itself if the child is kept off his feet for several months while suitable treatment is used.

Prophylaxis.—The light thrown by recent biochemical research on the maternal factor in rickets makes it clear that part of the prevention of rickets is antenatal and consists in proper feeding of the mother.

A mother who lives during pregnancy on bread, cheap margarine and tea, even with the addition of lean meat and potatoes, produces a child who is more prone to rickets than the offspring of a mother whose diet during that period has contained much milk, eggs and animal fat. The diet during pregnancy should also contain an adequate supply of calcium and phosphates; eggs and milk are large contributors of these.

The postnatal prevention of rickets depends almost entirely upon dietetic measures and chief of these is the provision of the "antirachitic factor" of fat-soluble vitamine. The proper and best source of this is the breast milk and the surest safeguard against rickets is the continuance of breast feeding alone for eight to nine months. Even breast milk may be deficient in fat-soluble vitamine if the mother's diet has not contained a sufficient quantity of it. If breast milk is not available, cow's milk is the best substitute provided again that the cows have been suitably fed. Milk should continue to be the chief article of diet until the end of the second year but other foods should be added after the age of eight to nine months.

It has often happened that an infant who is still at the breast but receives farinaceous food in addition has developed rickets. Experiments on puppies (Mellanby) have given similar results, and it would seem that in some way, especially when the supply of vitamine A barely exceeds the minimum requirement, the addition of farinaceous food favors the onset of rickets. This is sometimes explained by the allowing of much farinaceous food to the neglect of milk but it seems also to occur when the proportion of farinaceous food has been very small. The ill effect of farinaceous food is most marked when it is given in the earlier part of the first year; few infants are the better for any starch addition to the diet before the age of eight months. Even the small proportion of 2 per cent. of starch present in barley water seems to favor the occurrence of rickets and should be avoided; after eight months, starch may be introduced, but at first only in one meal, and by the time the child is ten months old in two meals daily. At nine months old, yolk of egg in small quantities, half a teaspoonful once daily makes a valuable addition to the diet and may be increased cautiously until, by the time that the child is a year old, the whole of the yolk of one egg is taken daily or several times a week. The yolk of egg, the antirachitic value of which was recognized many years ago, has now been shown experimentally to be rich in the antirachitic factor of vitamine A.

When there is risk of an insufficient supply of this antirachitic factor in the diet the simplest method of prevention is to give cod-liver oil; the quantity required is small, 15 drops three times daily is probably more than enough.

The liability to rickets becomes less after the end of the first year; most of the cases seen in the second year have had their onset within the first twelve months; for this reason the diet in the second year requires care as well as in the first. Milk should continue to be the staple diet, the child should take not less than one and a half pints daily, an egg should be given four or five times a week and butter should not be stinted. If margarine is used, it should be one of the better class margarines made

with animal fats. Fish, red gravy from roast meat, mashed potatoes, milk puddings and fruit juice, bread or rusks make up the rest of the diet.

Apart from diet the preventive value of *sunlight* is to be remembered, and as far as practicable the infant should be out in the sunlight; the living rooms should also as far as possible admit the direct rays of the sun; there is evidence that the antirachitic effect of sunlight is diminished when the rays have to pass through glass windows to reach the child.

Prevention of Deformities.—If rickets has appeared much may be done to prevent bending of the bones by such measures as avoid the pressure of the body or other weight upon the limbs. Standing and walking especially should be forbidden until the remedies, dietetic or otherwise, have had time to diminish the softness of the bones and the laxity of the ligaments and muscles. This may take several weeks. The greater vigor of the child's movements, the disappearance of sweating, and the increased activity of dentition, afford some indication of improvement; but in a general way with a marked degree of rickets, if the child has already begun to stand before the symptoms attract attention, he should be kept off his feet altogether for at least three months from the time the treatment is begun, and if standing has not yet been acquired the parents should not encourage the child to attempt to stand.

In severe rickets in the active stage even sitting should be discouraged, for apart from the kyphosis and lateral curvature, which are usually transitory, the occurrence of pelvic deformities is favored by the pressure from above and below incurred by the sitting position. In cases in which much deformity of the chest has occurred, with sinking in of the ribs in the axillary region and prominence of the sternum and cartilages, the danger of bronchitis and bronchopneumonia is to be remembered, and every precaution taken to avoid these complications.

Treatment.—In almost all cases the first point to be considered is the diet which usually requires rectifying on the lines indicated under the heading of prevention. Diminution or exclusion of starch, increase of milk and the addition of yolk of egg to the diet are the changes which are generally needed in accordance with the age of the child, and these alone would cure. But cure can be hastened by the administration of drugs, particularly cod-liver oil which was regarded as a potent cure for rickets many years before the vitamine theory was propounded; it has now been shown to be specially rich in the fat-soluble vitamine and particularly in the antirachitic factor. The properties of cod-liver oil in the treatment of rickets are possessed at least in equal degree by the oil from the liver of several other fishes. Vegetable oils, on the other hand, such as olive oil, peanut oil and cotton-seed oil, seem experimentally to have very little antirachitic value, though recent observations seem to show that these can in some way be induced with antirachitic properties by exposure to ultra-violet rays (Hess).

In some cases one of the combinations of malt extract with cod-liver oil is taken better; the admixture of malt seems to prevent that interference with digestion which sometimes results from cod-liver oil. Some children take cod-liver oil best in capsules. If cod-liver oil cannot be taken, yolk of egg is so rich in the antirachitic factor that it may be used as a substitute.

In some parts of Europe, especially in Vienna, but also in America by Jacobi, phosphorus has been strongly advocated. Opinions are much divided as to its value; some writers state that it is not only entirely without effect but that it produces gastro-intestinal disturbance and occasionally serious toxic symptoms. It seems probable that some, at least, of the benefit attributed to phosphorus, may have been due to the oil in which it has been given. It is often given dissolved in cod-liver oil; $\frac{1}{200}$ to $\frac{1}{100}$ grain (0.3 to 0.6 mg.) of phosphorus may be dissolved in 1 dram of cod-liver oil (4 cc.), and half this quantity given two or three times a day. Various other compounds of phosphorus have been used, particularly lecithin, preparations of hypophosphites in syrup, wheat phosphates, the soluble part of bran, and many patent preparations containing phosphorus. The syrupus ferri phosphatis of the British Pharmacopœia is used by many for rickety children over the age of twelve months; it is given in doses of $\frac{1}{2}$ to 1 dram (2 to 4 cc.). Glycerin extract of bone-marrow has given good results in some cases. Various organic remedies have been tried, but, in most observers' hands, have proved useless.

The value of *baths* is perhaps hardly sufficiently recognized; the child should have a warm bath at about 85° F. every morning, and while sitting in the bath should be douched with water at a slightly lower temperature, 75° to 80° F. If this is done with tact and the child gradually accustomed to it, there should be no dislike to it, and it seems to have an invigorating and tonic effect which may be of value especially in reducing the nervous instability.

If *convulsions* have occurred, or if a tendency to them is shown by laryngismus stridulus, tetany, or facial irritability, bromide should be given with cod-liver oil. Two to 4 grains (0.13 to 0.26 gm.) of potassium bromide in 1 dram (4 cc.) of cod-liver oil emulsion, are given three times daily. Sometimes chloral $\frac{1}{2}$ to 2 grains (0.032 to 0.13 gm.) is more effectual than bromide, and may be given every four to six hours.

Massage has been advocated and is likely to be useful in maintaining the nutrition of the muscles while it is necessary to keep the child off his feet; but it must be extremely gentle and is less applicable to infants under twelve months than to those who are older.

The child must be kept off its feet during the active stage, and if fat and heavy, especially if the bones of the legs already show bending, this measure may be necessary for several months. Often the only way to insure this is to apply long splints to the outer side of the legs, the splints being sufficiently long to project well beyond the sole of the foot. They should be removed when the child goes to bed so that it may kick its legs about freely and exercise its muscles as much as possible.

CONGENITAL RICKETS

It seems certain that rickets may be present at birth, but until recently cases of achondroplasia were described as fetal or congenital rickets, and, as Ballantyne has shown, there are several types of bone disease which occur *in utero*, all of which have probably been described as rickets in

the past. The relation of these to rickets is uncertain, but they bear so little resemblance to postnatal rickets, that it seems wise at present to consider them as something altogether distinct, although, as Ballantyne suggests, it may be that rickets occurring during intra-uterine life would be modified according to the period of development at which it occurred.

As to the frequency of congenital rickets, there is a wide discrepancy in statistics. Feyerabend at Königsberg, among 180 new-born infants, found 68.9 per cent. rickety. Schwarz in Vienna found that among 500 new-born infants, 80.6 per cent. showed rickets. Fede and Cacace, at Naples, among 500 new-born infants, found only 1 with clinical evidence of rickets, and in another series of 475 new-born infants, Fede and Finizzio found only 3 with rickets. Personal experience at the Children's Hospital, Great Ormond Street, suggests that within the first two months after birth rickets is excessively rare.

The symptoms are those described as characteristic of postnatal rickets, but the frequency of fractures in the long bones is a notable feature of the congenital disease. Often 4 or 5 of the bones are broken and the fracture is often complete, not green-stick. Monti quotes Chaussier as having found in one case, 42, in another 112 fractures. These are certainly not always produced during parturition for they have been found already united or in process of uniting at birth (Notta). All degrees of curvature of bones are also found. It has been stated that the rachitic distortions of the thorax are lacking in this form, but this is perhaps doubtful, for H. Ashby recorded a case in which the typical deformity of the rachitic chest was present at the age of fourteen days in association with several fractures in the limbs. Infants with congenital rickets are often of premature birth and are commonly feeble, so that the prognosis must be guarded. But so far as the fractures are concerned, the outlook is good; they unite rapidly after birth. With suitable feeding the rickets rapidly improves and may disappear entirely in a few months.

There has been extensive failure of ossification of the skull in several of the recorded cases, a defect which some have described as craniotabes. It is very doubtful, however, whether such a condition bears any relation to the localized patches of craniotabes mentioned as characteristic of ordinary rickets where the thinning of the skull is probably due to absorption rather than to defect of formation of bone.

To such cases the term "osteogenesis imperfecta" may be more applicable than rickets and in general it may be said that unless histological evidence is forthcoming much doubt attaches to supposed cases of congenital rickets.

Congenital rickets seems explicable by the vitamine theory. When for any reason, the mother has not taken a sufficient quantity of the foods which convey the antirachitic factor, the process of calcium deposit, which seems to be influenced by this factor, is hindered in the developing fetus. The fault in the mother's diet may date back sometime before the pregnancy began, for there is evidence that vitamines are stored to some extent, so that deficiency will only gradually result even when deprivation of vitamines is complete.

Treatment.—Clearly proper feeding of the mother both before and during pregnancy is important in the prevention of this affection in the newborn. When congenital rickets has occurred, the treatment, apart from suitable fixation of fractured bones, consists chiefly in proper feeding, at the breast if possible, otherwise with cow's milk upon the lines indicated above. The administration of cod-liver oil in doses of 10 to 15 m. (0.7 to 1 cc.) should be begun within the first week after birth.

LATE RICKETS

Rickets is occasionally seen as an active disease in the later period of childhood and in adolescence, and has then been described as late rickets, recrudescent rickets, or rachitis tarda. Probably the term recrudescent rickets most accurately describes the majority, for usually the patient has shown evidence of rickets in the first two years of life and after years of quiescence the disease has again started into activity. Much more rarely rickets makes its first appearance at this later period. Whether recrudescent or not, this late rickets is very rare; but it is said by some surgeons that adolescents at the period of rapid growth not infrequently show slight bending of bones, and this has by some been described as rickets. Apart from the curvature of bones, such cases usually show no other evidence of rickets and it seems very doubtful whether a mere failure of the hardening process in bone to keep pace with the rapid growth of bone at this age should be considered evidence of rickets. There is no doubt that bending of bones resembling that seen in rickets may occur quite apart from the histological characters of rickets, and if the histological changes at the epiphyses are to be regarded as mainly dependent upon the activity of growth at the age at which rickets mostly occurs, then it may be correct to regard rickets, late rickets and osteomalacia, as one and the same disease modified only by the age at which it occurs.[1]

Etiology and Pathology.—In attempts to produce rickets experimentally it has been noticed by many observers that while certain modes of dieting produce typical rachitic changes in the bones, others produce osteoporosis only. It has also been noticed that the characteristic epiphyseal rhachitic changes are much more readily induced in young and rapidly growing animals than in those older and less rapidly growing; in fact active growth would seem to be essential to the production of these particular rachitic manifestations.

It seems likely that dietetic faults, and perhaps even faults identical with those which produce typical rhachitic changes at the epiphyses in infants, may produce bending of bones and the less typical changes, mostly of osteoporotic nature, which have been described as "late rickets" in older children and adolescents.

Certainly deprivation more or less complete of foods which contain fat-soluble vitamine has been followed by the occurrence of bone softening with much bending and distortion at an age long past the usual age of

[1] Hutchinson, H. S., and Tapleton, Grace: *Brit. Jour. Dis. Children*, 1924, vol. **21.**

rickets. The writer observed such an occurrence in a girl of eight years who had for four years, during treatment for cœliac disease, been fed on a rigidly restricted diet, almost completely fat-free.

It has been stated that in some cases there has been no obvious fault in the diet but this may only mean that under the head of "late rickets" have been included conditions which were of entirely different nature. There is one in particular which has only been recognized within the last few years, namely, "renal infantilism." This condition is associated with

FIG. 106

marked bending of the bones and distortions near the epiphyseal junction and there can be little doubt that such cases were formerly mistaken for late rickets.

Late rickets has occurred most often between the age of nine and fourteen years, but it has begun as late as seventeen years. At what age rickets should be described as late, has not been settled. Probably the disease beginning or recrudescing after the age of four years, might properly be described thus.

Symptoms.—These are similar to those already described, but the onset has usually been with some pain in the limbs, more or less severe, especially in the legs. At the same time there has been weakness so that in some cases the patient has been unable to walk without assistance. The ribs become beaded and the epiphyses enlarged, as may be seen in Fig. 106, of a boy, aged nine and three-fourths years, in whom the symptoms of rickets, after remaining almost quiescent since his earliest years, became active again at the age of nine and a half years. He was under the care of my colleagues, R. Hutchison, and A. E. Garrod, at the Children's Hospital, Great Ormond Street. There was no enlargement of the head in this case, and this appears to be the rule; only 1 case has been recorded in which the head became enlarged during late rickets (James).

The thorax has become distorted in some cases with deformity described as typically rachitic. The bending of the lower limbs is sufficient generally to cause a waddling awkward gait. With the roentgen-rays, the bones give a less marked shadow than normal, presumably from deficiency of calcification.

Examination of the urine in one case (James) showed excessive excretion of lime (more than twice the normal). The amount of phosphoric acid was fully up to the normal but hardly excessive. Irregular pyrexia was noted in one case (Cautley) during the progressive stage.

Like rickets at an earlier age, the late form of the disease hinders growth and development, the establishment of puberty may be delayed, and the child remain undergrown. Hitherto no explanation of these cases of late rickets has been found. It has been stated in some cases that there was no obvious fault in the diet; in some cases a severe illness has preceded the onset.

Prognosis.—This must be guarded, for the deformity is often considerable; the disease is, however, rarely fatal. There seems to be less tendency to respiratory complications than in rickets during the first two years of life.

Treatment.—The treatment which has been found most effectual is similar to that used in ordinary rickets, namely, the administration of cod-liver oil, to which some have added phosphorus. After the disease has become quiescent, operative measures may be required for the correction of deformities, or apparatus, such as steel supports or splints, may be necessary to prevent further bending of the long bones.

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